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A MULTICENTRE, OPEN-LABEL EXTENSION STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND EFFICACY OF ORAL SB-207499 (15 MG TWICE DAILY) IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD). FINAL REPORT.

Clinical Study Report for Study SB-207499/040 (Development Phase III)

Document Code: GM2003/00558/00

Compound Number: SB-207499

Investigational Product: ARIFLO*

Generic Drug Name: Cilomilast

Indication Studied: Chronic obstructive pulmonary disease

Initiation Date: 14 June 1999

Data Cut-off Date: 19 September 2002

Date of Report: 28 April 2004

Earlier CSRs November 2002 (Interim Report)

Sponsor Signatory:
(and Medical Officer)

 Vice President, Respiratory Clinical Development and
Medical Affairs, GlaxoSmithKline

This study was performed in compliance with Good Clinical Practices including the archiving of essential documents.

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Synopsis

Document Number: GM2003/00558/00

Study ID: SB-207499/040

Title: A Multicentre, Open-label Extension Study to Evaluate the Safety, Tolerability and Efficacy of Oral SB-207499 (15 mg twice daily) in Patients with Chronic Obstructive Pulmonary Disease (COPD). Final Report.	
Investigators: Multicentre study.	
Study centres: The study was conducted in 130 centres in 10 countries (Australia, South Africa, Belgium, Finland, France, Germany, Netherlands, Norway, Spain and United Kingdom).	
Publications: There were no publications at the date of issue of this final report.	
Study period: 14 June 1999 to 19 September 2002.	Phase of Development: III
Objectives: The primary objective was to evaluate the long-term safety and tolerability of SB-207499 administered at a dosage of 15 mg twice daily in subjects with COPD. The secondary objective was to evaluate further the efficacy of SB-207499 in terms of pulmonary function, disease symptoms and quality of life	
Methodology: This was a multicentre, Phase III, open-label extension study in subjects with COPD. Subjects completing study 042 or study 091 were eligible for entry into this study. Subjects were given SB-207499 15mg twice daily and were required to attend the clinic after one, two, and four weeks and then at four-week intervals until at least 48 weeks. From Week 48 subjects transitioned to 12-week visit intervals (over a period up to Week 132 depending on timing of ethical approval) until study end. The study continued until termination by GlaxoSmithKline when it was considered sufficient safety data had been collected.	
Number of subjects: A total of 723 subjects participated in this study.	
Diagnosis and main criteria for inclusion: Male and female subjects with COPD who had successfully completed study 042 or study 091 without tolerability problems were enrolled into this study.	
Treatment administration: Study medication was provided as film-coated, octagonal, yellow "Tiltab" tablet containing 15mg of SB-207499. One tablet was taken in the morning and one in the evening, after a meal. Batch numbers were [REDACTED] and [REDACTED] and [REDACTED]	

Criteria for evaluation: Safety was evaluated by monitoring adverse experiences, laboratory parameters, 12-lead electrocardiograms (ECGs), vital signs, and physical examinations (including respiratory examinations). Efficacy variables were pulmonary function tests (trough forced expiratory volume in 1 second (FEV₁), forced expiratory volume in 6 seconds (FEV₆), forced expiratory flow at 25-75% of vital capacity (FEF₂₅₋₇₅), forced expiratory flow at 75% of vital capacity (FEF₇₅), forced vital capacity (FVC), peak expiratory flow rate (PEFR)), exercise tolerance test (6-minute walk test), dyspnoea assessments at rest, since the last visit, and after the exercise tolerance test, and COPD exacerbation rates. Health outcomes: the variables were St George's Respiratory Questionnaire (SGRQ), short form survey 36 (SF-36), and healthcare utilisation.

Statistical methods: Descriptive statistics were provided for demographic and baseline characteristics and safety parameters of clinical laboratory assessments, vital signs, and ECG interval. For efficacy parameters, the primary analysis was the within group change from the baseline assessment of the feeder studies 042 and 091. In addition, data from subjects randomised to placebo in study 042 or study 091 were analysed based on the change from Day 1 of study 040. Safety analyses were based on the population of subjects who received at least one dose of study medication. Efficacy analyses were based on the population of subjects who received at least one dose of study medication and had a baseline, a Day 1 and at least one post-Day 1 efficacy evaluation.

Summary:

Demographic Data: A total of 723 subjects were enrolled in study 040, 480 previously treated with SB-207499 from study 042 or study 091 and 243 previously treated with placebo from study 042 or study 091. At the baseline of the feeder studies, the two treatment groups were well matched for demographic characteristics and for baseline characteristics of COPD. Most subjects were male (84.2%) and white (98.5%) with an average age of 62.9 years. The subjects had a mean smoking history of 44.4 pack years. Current smokers made up 43.4% of the study population.

Safety: The mean duration of exposure to study medication was 744 days and 462 subjects had received treatment for ≥ 2 years. There were 677 subjects (93.6%) who reported on-therapy adverse experiences, the most common adverse experiences relating to the respiratory, gastrointestinal, and body as a whole systems. The most frequently reported adverse experience was chronic obstructive airways disease (i.e. COPD exacerbation) which occurred in 68.3% subjects. Other most frequently reported adverse experiences were abdominal pain (16.3%), diarrhoea (14.1%) and injury (13.1%). Gastrointestinal adverse experiences (abdominal pain, diarrhoea, nausea, dyspepsia) and headache occurred at a higher percentage in subjects who had previously taken placebo in study 042 and 091. This was associated with starting treatment with SB-207499. The majority of on-therapy adverse experiences, those occurring in approximately 67% of subjects, were of mild or moderate intensity.

There were 203 subjects (28.1%), 69 (28.4%) in the prior placebo group and 134 (27.9%) in the prior SB-207499 group, with on-therapy serious adverse experiences (SAEs). The most frequently occurring on-therapy SAE was chronic obstructive airways disease (i.e. COPD exacerbation), which occurred in 67 subjects (9.3%). Six subjects experienced SAEs considered to be possibly (suspected) related to study medication. Thirty-one subjects (4.3%) experienced post-therapy, SAEs.

Fifteen subjects died of events starting during the on-therapy study treatment period and 9 subjects died of events starting during the post-therapy period. None of the deaths was considered by the Investigator to be related to study medication.

During treatment with study medication, 97 subjects (13.4%) experienced gastrointestinal experiences (GIAEs) of concern, including 42 (17.3%) and 55 (11.5%) of subjects who had previously received placebo and SB-207499 in study 042 and 091, respectively. Overall, the two most common GIAEs were abdominal pain (6.1%) and diarrhoea (4.3%). These experiences occurred in a higher percentage of subjects who had previously received placebo.

Routine faecal occult blood testing resulted in a positive result for 35 subjects (5.7%)

Fourteen subjects were shown to have blood in their faeces in association with a GIAE of concern; 11 of these had blood observed in their stool. In addition, faecal occult blood testing revealed 4 subjects with a positive test result and one further subject with a positive test result at the safety follow-up visit after withdrawing for a GI haemorrhage. Of these 5 subjects, two also had overt blood in their stools and for three the stool appearance was not noted. There was no evidence for a treatment effect of SB-207499 on faecal occult blood results or clinically important changes in orthostatic vital signs in subjects experiencing GIAEs of concern.

A total of 123 subjects (17.0%) were withdrawn from the study due to an adverse experience.

The most frequent reasons for withdrawal were adverse experiences of the gastrointestinal system (45 subjects, 6.2%). The incidences of these and most other adverse experiences leading to subject withdrawal were greater in the group of subjects previously treated with placebo.

Overall, mean changes from baseline in laboratory values were small, and the percentage of subjects with laboratory values of potential clinical concern was low. There was no evidence for an adverse effect of SB-207499 on laboratory parameters. The percentages of subjects with transitions in sitting vital signs from normal at baseline to values of potential clinical concern on-therapy were low. Some changes in ECGs were observed during the study, but overall intensive 12-lead ECG monitoring did not raise any concerns about the cardiac safety of SB-207499.

Efficacy: The mean FEV₁ at baseline of study 042 and study 091 was 1.45 L for subjects randomised to placebo and 1.48 L for subjects randomised to SB-207499. At endpoint, the FEV₁ had decreased by a mean of 90 mL in the prior placebo group and 80 mL in the prior SB-207499 group as compared to baseline values of study 042 or study 091. Subjects switching from placebo to SB-207499 at the start of study 040 showed an increase in mean FEV₁ at the start of study 040.

In general, there were small decreases in mean FVC, PEF_R, FEF₂₅₋₇₅, FEF₇₅, and FEV₆ in both the prior placebo and the prior SB-207499 groups. Improvements in breathlessness score were seen in the early part of the study in both treatment groups. At endpoint, the overall breathlessness score had decreased from baseline in the prior SB-207499 treatment group, indicating an improvement in breathlessness relative to baseline, but there was an increase in the prior placebo treatment group. COPD exacerbation rates per subject year of follow-up were 1.396 for the prior placebo group and 1.307 for the prior SB-207499 group.

Health Outcomes: Improvements in SGRQ Total score were seen throughout the study period in both prior treatment groups. Effects were also seen on the symptoms, activities and impacts subscale scores. Some small effects were seen on some domains of the SF-36. For subjects in the prior placebo group, only very small changes from Day 1 in study 040 in SGRQ were seen at endpoint.

Healthcare utilisation was similar for the two prior treatment groups. The study design did not allow conclusions to be drawn, as there was no adequate control group.

Conclusions: Long-term treatment with SB-207499 15 mg twice daily was well tolerated with no new safety issues being identified. After a further 6 months of the study, results showed no substantial differences to those of the interim analysis. There was no evidence for any adverse effects of long-term drug administration on vital signs, ECG or laboratory variables. A small decline in FEV₁ was seen although this was smaller than might have been expected over this long-term treatment period. Improvements in health status were maintained over the study.

Date of Report: April 2004

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Abbreviations

μmol	Micromole
A	Age
A & AT	Archive and Access Technology
AE	Adverse Experience
ALP	Alkaline Phosphatase
ALT (SGPT)	Alanine Aminotransferase
AMP	Adenosine Monophosphate
AST (SGOT)	Aspartate Aminotransferase
ATS	American Thoracic Society
bd	Twice Daily
BMS	Biomedical Systems (Brussels, Belgium)
BP	Blood Pressure
bpm	Beats Per Minute
BTPS	Body Temperature, Pressure, Standard
BUN	Blood Urea Nitrogen
°C	Degrees Celsius
CI	Confidence Interval
COAD	Chronic Obstructive Airways Disease
COPD	Chronic Obstructive Pulmonary Disease
CRAMS	Case Report Form Activity System
CRF	Case Report Form
dBp	Diastolic Blood Pressure
dL	Decilitre
DRQ	Data Resolution Query
ECG	Electrocardiogram
EKG	Electrocardiogram
ER	Emergency Room
etc	et cetera
FDA	Food and Drug Administration
FEF ₂₅₋₇₅	Forced Expiratory Flow at 25-75% Vital Capacity
FEF ₇₅	Forced Expiratory Flow at 75% Vital Capacity
FEV ₁	Forced Expiratory Volume in 1 Second
FEV ₆	Forced Expiratory Volume in 6 Seconds
FOB	Faecal occult blood
FTP	File Transfer Protocol
FVC	Forced Vital Capacity
g	Gram
GCP	Good Clinical Practice
GGT/Gamma GT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
GIAE	Gastrointestinal Adverse Experience
GSK	GlaxoSmithKline
H	Height
Hb	Haemoglobin
HCG	Human Chorionic Gonadotropin
HR	Heart Rate

ICD-9	International Classification of Diseases – Revision 9
ICU	Intensive Care Unit
i.e.	that is
IEC	Independent Ethics Committee
IL	Interleukin
IRB	Institutional Review Board
IU	International unit
IUD	Intrauterine device
kg	Kilogram
L	Litre
LLN	Lower Limit of Normal
LOCF	Last Observation Carried Forward
LPS	Lipopolysaccharide
LTOT	Long-Term Oxygen Therapy
m	Metre
mEq	Milliequivalent
mg	Milligram
min	Minute
mL	Millilitre
mmol	Millimole
mmHg	Millimetres of mercury
msec	Millisecond
N	Number of subjects
NA	Not Applicable
NCS	No Clinical Significance
ND	Not Defined
NOS	Not Otherwise specified
NPN	Non-Protein Nitrogen
PDE4	Phosphodiesterase 4
PEFR	Peak Expiratory Flow Rate
PFT	Pulmonary Function Test
QTc	Corrected QT Interval
RAP	Reporting and Analysis Plan
R&D	Research and Development
SAE	Serious Adverse Experience
sBP	Systolic Blood Pressure
sd	Standard Deviation
SF-36	Short Form Survey 36
SGRQ	St. George's Respiratory Questionnaire
SI	Système Internationale
SNOMED	Systematized Nomenclature of Human (and Veterinary) Medicine
SQL	Standard Query Logic
SQRT	Square Root
TLCO	Carbon Monoxide Diffusing Capacity
ULN	Upper Limit of Normal
UQT	Uncorrected QT Interval
URTI	Upper Respiratory Tract Infection

US	United States
WBC	White Blood Cells
WHOART	World Health Organisation Adverse Reaction Terminology
Y	Years

Definitions

adverse experience	includes any noxious, pathologic or unintended change in anatomical, physiologic or metabolic functions as indicated by physical signs, symptoms and/or laboratory changes occurring in any phase of the clinical trial whether or not considered drug related
serious adverse experience	any experience which is fatal, life threatening, permanently or temporarily disabling or incapacitating or results in hospitalisation, prolongs a hospital stay or is associated with cancer or overdose (either accidental or intentional). In addition, any experience which the Investigator regarded as serious or which suggested any significant hazard, contraindication, side effect or precaution that may have been associated with the use of the drug was reported as serious
gastrointestinal adverse experience of concern	gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, vomiting) which cause the subject concern or interfere with usual activity (including eating and sleeping).
exacerbations of COPD	a worsening of COPD symptoms requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy. COPD exacerbations were categorised as Level 1, 2, or 3, based on the treatment received by the subject: Level 1 Exacerbation: Acute worsening of COPD that was self-managed by the subject at home by increasing usual COPD medications (i.e., the subject did not see a doctor for this episode). Level 2 Exacerbation: Acute worsening of COPD that required additional treatment (e.g., a short course of oral steroids, antibiotics, etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room). Level 3 Exacerbation: Acute worsening of COPD that required the subject to be admitted to the hospital for treatment.

1. ETHICS

1.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The study protocol, amendments, the informed consent, and any other information that required pre-approval were reviewed and approved by the appropriate combination of national, regional, or investigational centre Ethics Committee or Institutional Review Board prior to each centre's initiation.

1.2. Ethical Conduct of the Study

In accordance with any applicable country-specific regulations, GlaxoSmithKline (GSK) obtained approval from the appropriate regulatory agency before initiating the study in that country.

This study was conducted in accordance with “good clinical practice” (GCP) and all applicable regulations, including, where applicable, the Declaration of Helsinki, June 1964, as modified by the 48th World Medical Association, Republic of South Africa, October 1996.

1.3. Subject Information and Consent

Written informed consent was obtained from each subject prior to the performance of any study specific procedures. Case report forms (CRFs) were provided for each subject's data to be recorded.

The Investigator or his/her designee informed the subject or, where applicable, the subject's legally authorised representative (e.g. a parent, guardian, next of kin, other individual or other body with appropriate jurisdiction) of all aspects pertaining to their participation in the study.

The process for obtaining subject informed consent was in accordance with all applicable regulatory requirements. The Investigator or his/her designee and the subject or the subject's legally authorised representative both signed and dated the informed consent form before the subject participated in the study. The subject received a copy of the signed and dated form and the original was retained in the site study records. The decision regarding participation in the study was made by the subject and was entirely voluntary. The Investigator or his/her designee emphasised to the subject that consent regarding study participation may have been withdrawn at any time without penalty or loss of benefits to which the subject was otherwise entitled.

2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This was a multicentre study conducted in 130 centres in 10 countries (Australia, South Africa, Belgium, Finland, France, Germany, Netherlands, Norway, Spain and United Kingdom).

Monitoring of the study was undertaken by GSK personnel except in France and Spain. In France the monitoring was performed by Chiltern International (17/19 rue des Grandes Terres, 92508 Rueil Malmaison, France) and in Spain by MDS Pharma (Rosa de Lima 1-bis, Edificio Alba, 28290, Las Matas, Madrid, Spain). Monitoring clinic visits were made on a frequent basis at a mutually convenient time with advanced notification to study personnel prior to the clinic visit.

Data Management was performed by Quintiles, Dublin, Ireland.

Statistical analysis of the study data was conducted by the Statistics and Data Management group at GSK.

The laboratory samples were analysed by Dorevitch, Mayne Health Dorevitch Pathology, Heidelberg, Victoria, Australia, for all centres in Australia and by Quest Diagnostics, Heston, Middlesex, UK (formerly SmithKline Beecham Clinical Laboratories) for centres in all other countries.

Centralised spirometry and electrocardiogram (ECG) services were provided by Biomedical Systems, Brussels, Belgium.

The study medication was provided by Clinical Trial Supplies Department of GSK Research and Development.

The report authors were [REDACTED] (Respiratory Clinical Development and Medical Affairs), [REDACTED] (Respiratory Clinical Development and Medical Affairs), [REDACTED] (Biomedical Data Sciences), [REDACTED] (Global Safety and Pharmacovigilance), [REDACTED] (Global Health Outcomes).

3. INTRODUCTION

SB-207499 (cilomilast) is a potent and selective phosphodiesterase type 4 (PDE4) inhibitor currently under development for the treatment of chronic obstructive pulmonary disease (COPD).

COPD is a multi-faceted, progressive respiratory disorder, characterised by a reduction in expiratory flow, which is largely irreversible to bronchodilators and slow forced emptying of the lungs, features which do not change markedly over several months [Siafakis, 1995].

The World Health Organisation (WHO) estimates the prevalence of COPD to be 600 million world-wide, with approximately 3 million deaths being recorded due to COPD in 1993. Although it is currently the fifth greatest cause of mortality world-wide, COPD is projected globally to become the third leading cause of mortality and the fifth leading cause of morbidity over the next 20 years [Murray, 1997; Viegi, 2001].

The main risk factor for COPD is inhalation of tobacco smoke although exposure to occupational dusts and chemicals, air pollutants and infections are also known risk factors [GOLD, 2001]. The disease has a considerable impact on patient's health status leading to severe disability and premature death. Chronic, progressive symptoms (breathlessness, wheezing, cough and sputum production) and disruption caused by exacerbations progressively limit normal activities. Exacerbations of COPD are a major cause of morbidity and mortality and are closely associated with symptomatic and physiological deterioration [Osman, 1997; Rutgers, 2000; Seemungal, 1998].

Inflammation and damage of the lung alveoli, play a central role in the reduction in expiratory flow and slow forced emptying of the lungs. There is an increase in inflammatory cells in the airways with a predominance of CD8+ T-lymphocytes and alveolar macrophages (CD68+ cells) in the sub-epithelium and increased neutrophils in induced sputum and bronchoalveolar lavage fluid [Jeffery, 1998] [Ronchi, 1996; Riise, 1995]. It has been demonstrated that there is a significant correlation between decreased FEV₁ and the numbers of CD8+ T-lymphocytes and macrophages in patients with COPD [Lams, 2000; O'Shaughnessy 1997]. Furthermore, significant correlations have also been demonstrated between increased numbers of CD8+ T-lymphocytes and increased bronchial hyperresponsiveness [Rutgers, 2000], and the number of packed years smoked [Lams, 2000].

There is currently no cure for COPD. Current treatment modalities for COPD include smoking cessation, long-term oxygen therapy (LTOT), pulmonary rehabilitation, ventilatory support, surgery, and pharmacological therapies [Siafakis, 1995; American Thoracic Society (ATS), 1995b; GOLD, 2001]. All of these have their limitations and so treatment options still remain limited.

Considering that inflammation is a major hallmark of COPD and contributes to its pathophysiology and clinical manifestation, its treatment should represent a major target for pharmacological therapy.

The rationale for the use of PDE4 inhibitors in the treatment of COPD is based upon the role of cyclic adenosine monophosphate (cyclic AMP) as a second messenger that mediates a broad suppression of immune and inflammatory cell activity, along with the knowledge that PDE4 is the major cyclic AMP-hydrolysing isozyme in these cells [Torphy, 1991]. It is established that elevation of cyclic AMP (cAMP) levels within the cells of relevant tissues results in (i) broad suppression of inflammatory activity, (ii) airway smooth muscle relaxation, (iii) suppression of smooth muscle mitogenesis, and (iv) modulation of excitatory activity in pulmonary nerves [Barnette, 1999], all effects that are applicable to the pathological processes that characterise COPD.

SB207499 has been demonstrated to be a potent and selective phosphodiesterase 4 (PDE4) inhibitor in a variety of in-vitro animal models showing. These point to is efficacy in the suppression of recruitment and activation of a variety of inflammatory mediators. In a guinea-pig model of inhaled LPS (lipopolysaccharide)-induced pulmonary neutrophilia and oedema, orally administered SB-207499 reduced both of these inflammatory parameters to a degree that rivals that of high-dose, orally administered prednisolone. In another *in vivo* guinea pig model, SB-207499, applied directly to the luminal side of the trachea, virtually abolished interleukin- (IL-) 8-driven neutrophil infiltration and goblet cell degranulation. In addition to its effects on neutrophil function, SB-207499 has bronchodilating properties and the capacity to modulate aberrant excitatory neuronal input to the airways. These actions may contribute to an overall beneficial effect in COPD, particularly with respect to improving small airway function [GSK Document Number SB-207499/RSD-100ZL5/4].

Previous non-selective phosphodiesterase inhibitors, such as theophylline, and subsequent PDE4 inhibitors, such as rolipram and BRL 61063, have been associated with limiting side effects commonly manifested as nausea, vomiting, enhanced gastric acid secretion, and psychotropic activity, such as agitation and restlessness, with higher doses producing convulsions. In pre-clinical models, data suggested that SB-207499 would be less likely to have such effects at concentrations that are associated with anti-inflammatory activity.

The clinical experience with SB-207499 in subjects with COPD includes two Phase II studies, four pivotal Phase III studies and three Phase III supporting studies giving a total of 2586 subjects on SB207499 and 1507 subjects in placebo groups. Two open label extension studies, of which study 040 is one, exposed another 383 former placebo patients to active medication. Phase II development consisted of two double-blind, placebo-controlled studies. Study 032 [GSK Document Number SB-207499/RSD-100J42/2] was of 6 weeks duration and evaluated SB-207499 at dosages of 5, 10 and 15mg twice daily (bd) with meals. Study 038 [GSK Document Number SB-207499/RSD-100J49/1] investigated lower dosages of 2.5 and 5mg twice daily for 4 weeks. Results of study 032 clearly demonstrated a beneficial effect of SB-207499 at a dosage of 15mg twice daily in subjects with COPD. Consistent statistically significant differences from placebo were seen in subjects who received SB-207499 15mg twice daily for changes from baseline in pre-bronchodilator trough forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), and peak expiratory flow rate (PEFR) at endpoint (last on-therapy measurement) and at 4 hours after the first dose. In addition, reductions in dyspnoea (exertional and at rest) and beta₂-agonist use were supported by

trends for improvement in quality of life for subjects who received 15mg twice daily. Increased incidence of gastrointestinal adverse events in healthy volunteers at doses above 15mg bd suggested that this was the maximum tolerated dose .

The Phase III COPD program consisted of four pivotal Phase III studies (studies 039, 042, 091, and 156). Subjects completing study 039 had the option of receiving open label medication with SB-207499 (15mg twice daily) in the extension study 041 (US and Canada). Subjects completing studies 042 and 091 had the option of receiving open label medication with SB-207499 (15mg twice daily) in the present extension study, 040 (Europe, South Africa and Australia). The present study, study 040, evaluated the long-term safety, tolerability, and efficacy of SB-207499. Prior to enrolment in study 040, subjects had to have completed either study 091, where subjects received SB-207499 15mg twice daily or placebo for 26 weeks, or study 042, where subjects received SB-207499 15mg twice daily or placebo for 24 weeks. Study 042 and study 091 have been reported [[GSK Document Number SB-207499/RSD-100TKX/1](#) and [GSK Document Number SB-207499/RSD-1017SH/1](#), respectively).

Study 040 continued until GlaxoSmithKline considered that sufficient safety data had been collected and that the funding could be better used further to investigate specific safety issues. An interim report [[GSK Document Number SB-207499/RSD-1017MT/1](#)] was produced in November 2002. This is the final report for the study, presenting data collected from subjects up to the end of the study on 19 September 2002.

Studies currently underway include Phase IIIA registration studies 107 and 122 (Japan), 121 (China) and 157 (Europe) plus Phase IIIB studies: 125 (co-administration of Cilomilast with Seretide); 180 (hyperinflation) and study 181 (biopsy study looking at inflammatory markers in the lung)

4. STUDY OBJECTIVE(S)

4.1. Primary Objective

The primary objective of this study was to evaluate the long-term safety and tolerability of SB-207499 administered at a dosage of 15mg twice daily in subjects with COPD.

4.2. Secondary Objective

The secondary objective of this study was to evaluate further the efficacy of SB-207499 in terms of pulmonary function, disease symptoms, and quality of life.

5. INVESTIGATIONAL PLAN

5.1. Study Design

5.1.1. Overall Study Design - Description

This was a multicentre, Phase III, open-label, single group extension study in subjects with COPD. All subjects received treatment with SB-207499 15mg twice daily (bd). The study was terminated by the sponsor during July to September 2002 as it was considered that sufficient safety data had been collected and that the funding could be used to look at specific safety issues. Subjects generally withdrew at a 12-weekly visit from July 2002 with the final patient completing the safety follow up visit by 19 September 2002. (In Norway, the study duration was restricted to 96 weeks).

At study start, subjects with COPD who completed study 042 or 091 and satisfied additional inclusion and exclusion criteria were eligible to enter study 040 of SB-207499 at a dosage of 15mg twice daily. Subjects were assessed for their eligibility for study 040 at their final scheduled visit of study 042 at Week 24, or study 091 at Week 26 (i.e. prior to Safety Follow-up visit). The study blind from the previous studies was not broken before entering into study 040.

During the treatment period, subjects attended the clinic after one, two, and four weeks and then at 4-weekly intervals until at least Week 48, followed by 12-weekly visits until the end of the study. Subjects were asked to return for a follow-up visit one to two weeks after the last visit on open-label treatment. Initially subjects had been scheduled to attend for 4-weekly visits throughout the study; this was reduced to 12-weekly visits after Week 48 or later, with the implementation of protocol amendment 2. To ensure that data was collected from all subjects at the same timepoints, 12-weekly visits were only initiated after a visit at a 12-weekly interval had been performed (i.e. only after Week 48, Week 60, Week 72 etc.). Patients had generally completed their transition to 12-weekly visit intervals by Week 96. However, due to delays in submitting protocol amendment 2 in Spain the last patient did not transfer to 12-weekly visits until Week 132 Visit 36.

On non-visit days, study medication was to be taken orally, twice daily, in the morning after breakfast and in the evening after a meal. On visit days, subjects refrained from taking their medication for at least 8 hours prior to their appointment. Visits were scheduled at about the same time of day (± 2 hours), ideally at 10am. Alternative times were permitted including afternoon visits but the time of the visit was to remain stable for the duration of the study. Subjects should have refrained from smoking, taking short acting beta₂-agonists or anticholinergics for at least 2 hours prior to presentation to clinic. Long acting beta₂-agonists should not have been taken for at least 12 hours prior to presentation to clinic.

Subjects who entered study 040 from study 042 took their final dose of study 042 medication in clinic prior to entering study 040 and took their first dose of 040 study medication after their evening meal, allowing at least 8 hours since the time of the last

dose of study medication taken in the clinic. Subjects who entered study 040 from study 091 took their first dose of 040 study medication at their first clinic visit.

All other COPD medications (with the exception of theophylline and aminophylline (oral and intravenous)) were permitted without restriction for all subjects in study 040. Where possible, other COPD medications were to be administered at a stable dose.

The assessments performed at each visit are shown in [Table 1](#).

Table 1 Study Procedures at Each Visit

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Early Withdrawal	Follow-up Final Visit +1 week
Time relative to baseline (weeks)	Baseline 0	+1	+2	4	8	12	16	20	24	28	32	36	40	44	48		
Signed written informed consent	x																
Study medication compliance		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant medication	x ¹	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Diary card review ⁷		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse experiences ⁸	x ¹	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
COPD exacerbation assessment/ healthcare utilisation	x ¹	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical (including respiratory) examination	x ¹								x						x	x	x ²
Resting 12-lead ECG	x ¹	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x ²
Vital signs (BP, HR) ³	x ¹	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Overall Breathlessness (modified Borg)	x ¹		x	x	x	x	x	x	x	x	x	x	x	x	x		
Exercise tolerance test (6-minute walk)	x ¹					x			x			x			x		
Post-exercise breathlessness	x ¹					x			x			x			x		
Pulmonary function tests ⁴	x ¹		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Laboratory tests ⁵	x ¹	x	x	x	x	x	x	x	x ⁵	x	x	x	x	x	x ⁵	x	x ²
Pregnancy test ⁶	x ¹			x	x	x	x	x	x	x	x	x	x	x	x	x	x
Quality of life assessments: SGRQ	x ¹					x			x						x	x	
Quality of life assessments: SF-36	x ¹								x						x	x	
Dispense or re-dispense open-label medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Study conclusion record																x	

Continued

Table 1 Study Procedures at Each Visit (Continued)

Visit	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33		
Time relative to baseline (weeks)	52*	56*	60	64*	68*	72	76*	80*	84	88*	92*	96	100*	104*	108	112*	116*	120	Early Withdrawal	Follow-up Final Visit +1 week
Study medication compliance	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Diary card review ⁷	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse experiences ⁸	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
COPD exacerbation assessment/ healthcare utilisation	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical (including respiratory) examination						x						x						x	x	x ²
Resting 12-lead ECG	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x ²
Vital signs (BP, HR) ³	x	x	x	x	x	x	x	x	x	x	x	x ³	x	x	x	x	x	x	x ³	x
Overall Breathlessness (modified Borg)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Exercise tolerance test (6-minute walk)			x			x			x			x			x			x		
Post-exercise breathlessness			x			x			x			x			x			x		
Pulmonary function tests ⁴	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Laboratory tests ⁵	x	x	x	x	x	x	x	x	x	x	x	x ⁵	x	x	x	x	x	x	x ⁵	x ²
Pregnancy test ⁶	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Quality of life assessments: SGRQ						x						x						x	x	
Quality of life assessments: SF-36						x						x						x	x	
Dispense or re-dispense open-label medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Study conclusion record																			x	

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Table 1 Study Procedures at Each Visit (Continued)

Visit	34	35	36	37	38	Early Withdrawal	Follow-up Final Visit +1 week
Time relative to baseline (weeks)	124*	128*	132	144	156		
Study medication compliance	x	x	x	x	x	x	
Concomitant medication	x	x	x	x	x	x	x
Diary card review ⁷	x	x	x	x	x	x	
Adverse experiences ⁸	x	x	x	x	x	x	x
COPD exacerbation assessment/ healthcare utilisation	x	x	x	x	x	x	x
Physical (including respiratory) examination				x**		x	x ²
Resting 12-lead ECG	x	x	x	x	x	x	x ²
Vital signs (BP, HR) ³	x	x	x	x ³	x	x ³	x
Overall Breathlessness (modified Borg)	x	x	x	x	x		
Exercise tolerance test (6-minute walk)			x	x	x		
Post-exercise breathlessness			x	x	x		
Pulmonary function tests ⁴	x	x	x	x	x	x	x
Laboratory tests ⁵	x	x	x	x ⁵	x	x ⁵	x ²
Pregnancy test ⁶	x	x	x	x	x	x	x
Quality of life assessments: SGRQ				x**		x	
Quality of life assessments: SF-36				x**		x	
Dispense or re-dispense open-label medication	x	x	x	x	x		
Study conclusion record						x	

BP=Blood Pressure, HR=Heart Rate, SGRQ=St George's Respiratory Questionnaire, SF-36=Short Form Survey 36.

1. Assessed during Visit 10, final double-blind visit, of study 042 and visit 11 of study 91 (except the health status assessments for study 091 which were performed at visit 10).

2. Only if abnormalities were present at the previous visit.

3. Orthostatic blood pressure and heart rate were measured at 24 weeks, 48 weeks and 48-weekly thereafter. Also at Early Withdrawal.

4. To include FEV1, FEV6, FVC, FEF25-75, FEF75, and PEF75.

5. Faecal occult blood (FOB) was measured at 24 weeks, 48 weeks and 48-weekly thereafter. Also at Early Withdrawal and if subject experiences GIAE of concern. Baseline measure was taken from last FOB in study 042 or study 091.

6. Serum pregnancy test for female subjects of child-bearing potential. Urine test was only done at Follow-up Visit.

7. A Diary Card was issued at each visit. The subject used the Diary Card to record if they felt differently since the previous visit

8. Subjects were assessed for GIAEs at every visit.

* Visit not performed once subject had switched to 12-weekly visits.

** Measured every 24 weeks thereafter.

5.1.2. Discussion of Study Design, Including the Choice of Control Group(s)

A multicentre, open-label continuation study was chosen to assess the long-term safety, tolerability, and clinical efficacy of SB-207499 in subjects with COPD. Because this was an open-label study, there was no control group.

5.2. Protocol Amendments

The protocol was initially issued on 12 March 1999 and four amendments were issued on 19 August 1999, 15 November 2000, 23 February 2001 and 12 April 2001.

Amendment 1, issued on 19 August 1999, affected centres in Norway only and limited the duration of treatment with study medication to 96 weeks.

Amendment 2 issued on 15 November 2000, applied to centres in all countries except Norway, and reduced the frequency of visits from 4-weekly to 12-weekly once subjects had completed at least 48 weeks in the study. In order to ensure that data was collected from all subjects at the same timepoints, subjects commenced 12-weekly visits only after a visit at a 12-weekly interval had been performed (i.e. only after Week 48, Week 60, Week 72, Week 84, etc).

Modification 1 issued on 27 November 2000 provided for dispensing of study medication at 12-weekly intervals, in accordance with Amendment 2.

Amendment 3, issued on 23 February 2001, applied to centres in Norway only. It sought to extend the duration of the study from 96 weeks to allow it to continue until SB-207499 was registered in the country or until the study was terminated by the sponsor. It also reduced the frequency of visits from 4-weekly to 12-weekly once subjects had completed at least 48 weeks in the study. This amendment was rejected by the Ethics Committee in Norway and so was not implemented.

Amendment 4, issued on 12 April 2001, applied to all centres in all countries. Following a request from the US Food and Drug Administration (FDA), it added the requirement that subjects who experienced a gastrointestinal adverse experience of concern and who had a positive faecal occult blood test, should be referred to a gastroenterologist for a complete colonoscopy, including visualisation of the transverse colon. Biopsies were to be taken if appropriate. In addition, more detailed instructions were provided for the performance of faecal occult blood tests.

Before granting approval for Amendment 4 and also permitting subjects to remain in the study for an additional year, the [REDACTED] asked for submission of a qualified statement providing GSK's assessment of the risk-benefit profile of SB-207499. Therefore some subjects at centres in Germany were required to discontinue the study while waiting for this approval to be obtained.

5.3. Selection of Study Population

Male and female subjects with COPD who had successfully completed study 042 or study 091 without tolerability problems were enrolled into this study.

5.3.1. Inclusion Criteria

Subjects who fulfilled the following criteria were eligible for inclusion in the study.

1. Males or females with COPD who had successfully completed study 042 or study 091 where subjects received SB-207499 15 mg bd or placebo for 24 weeks in study 042 and 26 weeks in study 091 without tolerability problems.

Women of childbearing potential were to have been using effective contraceptive measures (i.e., oral contraceptives, Norplant[†], an intrauterine device (IUD), a diaphragm with spermicide, a condom with spermicide, or Depo-Provera[†]) prior to Visit 1 and were to continue using the same contraceptive measure during the study.

2. Subjects who had given their written informed consent to participate.

5.3.2. Exclusion Criteria

Subjects who fulfilled any of the following criteria **were not** eligible for inclusion into the study:

1. Women who were pregnant or lactating, or who were planning for pregnancy within the next 24 months.
2. Subjects who had withdrawn from study 042 or study 091 for any reason.
3. Subjects who had a positive faecal occult blood test between Weeks 20 and 24 in study 042 or study 091.
4. Subjects who had experienced a serious adverse experience, a gastrointestinal adverse experience or a clinically significant laboratory abnormality, which in the opinion of the Investigator could have been attributed to study medication, during study 042 or study 091 and which was still present at the end of either study.
5. Subjects who in the opinion of the Investigator were not suitable for enrolment into the study.

5.3.3. Predetermined Criteria for Subject Withdrawal

Premature termination was defined as withdrawal of the subject for any reason before registration of the compound or project termination. Some subjects were withdrawn from the study due to lack of approval from Ethics Committees to continue the study beyond 96 weeks. These subjects were deemed to have completed the study.

A subject could have been withdrawn for any of the following reasons:

- **Adverse experience:** This included a deterioration in COPD or COPD exacerbation resulting in a subject being withdrawn.

[†] Norplant is a registered Trademark for Levonorgestrel.

[†] Depo-Provera is a registered Trademark for medroxyprogesterone acetate by Pharmacia.

- **Lack of efficacy:** This included a desire by the subject/Investigator that the subject be withdrawn from the study because of no improvement in COPD symptoms. It did not include deterioration in COPD or COPD exacerbation which was regarded as an adverse experience.
- **Conduct of study deviation:** This was for a significant protocol deviation including lack of compliance.
- **Subject lost to follow-up**
- **Termination** of the study by GSK.
- **Other:** The specific reason was documented in the CRF.

All adverse experiences leading to withdrawal of a subject were fully documented and followed-up as appropriate.

5.4. Investigational Product(s)

5.4.1. Description of Investigational Product(s)

SB-207499 was provided as film-coated, octagonal, yellow “Tiltab” tablets containing 15mg of SB-207499. The appearance, formulation, and batch numbers of the study medication are presented in [Table 2](#).

Table 2 Appearance, Formulation and Batch Numbers of Study Medication

Study Drug	Appearance	Formulation	Dose Unit	Batch Numbers		Expiry Date ¹
SB-207499	Yellow, octagonal	“Tiltab” tablet	15mg	[REDACTED]	[REDACTED]	09/2001
				[REDACTED]	[REDACTED]	04/2001 (extended to 30 Apr 2002)
				[REDACTED]	[REDACTED]	31 Oct 2004
				[REDACTED]	[REDACTED]	31 Oct 2004
				[REDACTED]	[REDACTED]	31 Jan 2006

1. Expiry date at time supplies packed

Batch numbers [REDACTED] and [REDACTED] were manufactured by GSK Crawley (Magpie Wood, Manor Royal, Crawley, Sussex, UK) and batch numbers [REDACTED] and [REDACTED] were manufactured by GSK Cidra (GSK Pharmaceuticals, Road 172 Km 9.1, PO Box 11975, Cidra, Puerto Rico).

Study medication was supplied in bottles containing either 70 or 210 tablets, providing a 35-day or 105-day supply of study medication. Study medication was issued at each clinic visit.

Subjects retained their patient identification number from study 042 or study 091. Study medication labels for all subjects did not have pre-printed patient identification numbers.

Investigators transcribed the subject initials, date dispensed and visit number for the subject onto the study medication labels.

A two-panel label consisting of a fixed portion and a tear-off portion was attached to the medication bottles. The Investigator (or designate) removed the tear-off portion of the label from the bottle at the time of dispensing and attached it to the appropriate page in the CRF.

Labels contained:

- Space to enter subject initials.
- Space to enter date dispensed.
- Space to enter visit number.
- Description of contents.
- Protocol number.
- Dosing directions.
- Storage conditions (room temperature).
- Packaging (job) number.
- Batch number of tablets.
- Keep out of reach of children.
- Appropriate caution statements.
- Company address.
- Any other information specified by local regulatory requirements.

Prior to dispensing, all study medication was kept safely locked, in a dry place at room temperature. For batches [REDACTED] and [REDACTED] this was defined as at or below 30°C. For batches [REDACTED] [REDACTED] and [REDACTED] the storage conditions were between 20-25°C which is in line with room temperature storage as defined by the US FDA.

5.4.2. Dosages and Administration

Subjects took one tablet in the morning after breakfast (ideally at 08:00) and one tablet after their evening meal (ideally at 20:00).

Tablets were ingested with a glass of water. At each visit, subjects were instructed by the Investigator to attend the next visit not having taken the pre-clinic dose of study medication. These doses were taken during the clinic visits (with food) at the instruction of the Investigator. Subjects who attended afternoon visits would take the morning dose of medication and attend clinic at least 8 hours later.

The first dose of study medication for subjects transferring from study 042 was not taken at the first clinic visit of study 040. Instead, subjects took the first dose of study 040

medication in the evening allowing at least 8 hours since the last dose of study 042 medication taken in the clinic that morning.

5.4.3. Dose Rationale

Study 032 [[GSK Document Number SB-207499/RSD-100J42/2](#)] was a 6-week study to evaluate SB-207499 at dosages of 5, 10 and 15mg twice daily. Results of study 032 clearly demonstrated a beneficial effect of SB-207499 at a dosage of 15mg twice daily in subjects with COPD. Consistent, statistically significant differences from placebo were seen in subjects who received SB-207499 15mg twice daily for changes from baseline in pre-bronchodilator trough forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), and peak expiratory flow rate (PEFR) at endpoint (last on-therapy measurement) and at 4 hours after the first dose. In addition, reductions in dyspnoea (exertional and at rest) and beta₂-agonist use were supported by trends for improvement in quality of life for subjects who received 15mg twice daily. Changes from baseline for subjects who received lower dosages of SB-207499 were not significantly different from placebo. A dose of 15mg was considered to have the best benefit risk ratio.

5.4.4. Blinding

The study blind from the feeder studies was not broken before subjects entered study 040. Blinding was not necessary for this study because this was an open-label continuation study in which all subjects received SB-207499.

5.4.5. Treatment Assignment

This was an open-label, non-comparative study. All subjects received 15mg SB-207499 twice daily throughout their participation in this study.

5.4.6. Assessment of Compliance

Counts of tablets returned were made at the beginning of all visits. Percent compliance was calculated by using the formula below and was entered into the CRF:

$$\frac{\text{Number of tablets dispensed} - \text{number of tablets returned or lost}}{2 \times \text{number of days since last visit}} \times 100$$

Subjects showing a compliance of <80% or >120% in taking study medication at two consecutive visits were not permitted to continue in the study.

5.4.7. Treatment of Investigational Product Overdose

Treatment of any suspected or confirmed overdose with SB-207499 was to be symptomatic. GSK did not recommend any specific treatment, and the Investigator used clinical judgement in treating the overdose. Any instance of a suspected or confirmed overdosage was fully documented as a serious adverse experience.

5.5. Prior and Concomitant Medications and Non-Drug Therapies

All concomitant medication taken during the study was recorded in the CRF with the indication, unit dose, frequency and dates of administration.

The use of on-demand inhaled beta₂-agonists was permitted throughout the study on an “as needed” basis. Subjects continued to use the beta₂-agonists they had been using before the study. The use of anticholinergic medication was also permitted during the study. Subjects continued to use their regular inhaler devices. Where possible, the dose of the medication remained stable throughout open-label treatment. All other COPD medications with the exception of theophylline and aminophylline (oral and intravenous) were permitted without restriction during the study and, whenever possible, doses were to remain stable.

5.6. Study Assessments and Procedures

For each scheduled study visit, subjects were required to attend the clinic in the morning, at about the same time of day preferably at 10:00 a.m. $\pm$ 2 hours. Subjects were requested not to take the morning dose of study medication before the visit and to refrain from using beta₂-agonists (short-acting), anticholinergic medications, and from smoking during the 2-hour period preceding the visit and from using beta₂-agonists (long-acting) during the 12-hour period preceding the visit. Smoking and the use of beta₂-agonists or anticholinergic treatment were to be avoided during the clinic stay if at all possible.

If, in exceptional circumstances, the subject attended afternoon appointments, he/she was instructed to take the morning dose of study medication after breakfast, and attend the clinic visit at least 8 hours later. Those subjects who attended afternoon visits were requested to attend at a similar time $\pm$ 2 hours for all visits.

The outline of study procedures is presented in [Table 1](#) in Section [5.1](#).

5.6.1. Demographic and Baseline Assessments

Eligible subjects entered study 040 at their final “On-therapy” Visit of study 042 or 091 (i.e., Visit 10 for study 042 and Visit 11 for study 091). There was to be no gap between completing the preceding study and entering study 040. Data from Visit 10 in study 042 or Visit 11 in study 091 were used as the data for Visit 1 in study 040.

Demographic and baseline assessments in this study were taken from those recorded in the feeder studies 042 and 091.

5.6.2. Safety Assessments

Safety was evaluated by:

- monitoring adverse experiences (including COPD exacerbations and gastrointestinal adverse experiences)

- physical examination (including respiratory examination)
- resting 12-lead ECGs
- vital signs
- laboratory parameters

5.6.2.1. Adverse Experiences

An adverse experience included any noxious, pathological or unintended change in anatomical, physiological or metabolic functions as indicated by physical signs, symptoms and/or laboratory changes occurring in any phase of the clinical study, whether or not considered drug related. This included an exacerbation of pre-existing conditions or experiences, intercurrent illnesses, drug interaction or the significant worsening of the disease under investigation that was not recorded elsewhere in the CRF under specific efficacy assessments. Anticipated day-to-day fluctuations of pre-existing conditions, including the disease under study, that did not represent a clinically significant exacerbation or worsening were not considered adverse experiences. Discrete episodes of chronic conditions occurring during a study period were reported as adverse experiences in order to assess changes in frequency or severity.

Any pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study were recorded on the Medical/Surgical History form within the subject's CRF for either study 042 or study 091. All adverse experiences that were ongoing at the end of either study 042 or study 091 were transcribed into the 040 CRF with the same start date. All adverse experiences occurring after administration of the first dose of open-label study medication and on or before the final visit were reported on the Adverse Experience pages in the CRF, whether or not they were considered to be drug related. Exacerbations of COPD were recorded as adverse experiences in a separate section of the CRF.

Adverse experiences were elicited by the Investigator asking the subject a non-leading question such as "Have you felt different in any way since starting the new treatment or since the last visit?" In order to help the subject to remember and to answer this question accurately, a diary card was provided with space in which the subject could record if they felt different since starting the study medication. If the subject responded "Yes" to the question, the nature of each experience, date and time (where appropriate) of onset, outcome, course (i.e., intermittent or constant), maximum intensity, action taken with respect to the investigational drug and relationship to treatment were established. Details of changes to the dosage schedule or any corrective treatment were recorded on the appropriate pages of the CRF. Attribution or relationship to study drug was judged by the Investigator to be not related, unlikely, suspected (reasonable possibility) or probable. The maximum intensity of the adverse experience was rated as mild, moderate or severe.

Adverse experiences already documented in the CRF (i.e., at a previous visit and designated as ongoing) were reviewed at subsequent visits as necessary. If these had resolved, the documentation in the CRF was completed. If an adverse experience increased in frequency or severity during a study period, a new record of the experience was started.

5.6.2.2. Serious Adverse Experiences

Serious adverse experiences that occurred at any time during the study or within 30 days of receiving the last dose of study medication, whether or not related to study drug, were required to be reported to the GSK Medical Monitor within 24 hours and followed by a full written report. A serious adverse experience was defined as any experience which was fatal, life threatening, disabling or incapacitating or resulted in hospitalisation, prolonged a hospital stay or was associated with congenital abnormality, cancer or overdose (either accidental or intentional). In addition, any experience which the Investigator regarded as serious or which suggested any significant hazard, contraindication, side effect or precaution that may have been associated with the use of the drug was documented as a serious experience.

5.6.2.3. Pregnancies

All women of child-bearing potential were required to have a serum pregnancy test at all visits and a urinary pregnancy test at the Follow-up Visit. Any subject who became pregnant was to be withdrawn immediately from the study.

Any pregnancies were to be followed to term, any premature terminations reported and the status of mother and child after delivery reported to GSK. Investigators were to notify GSK if it was determined after completion of the study that a subject became pregnant either during the treatment phase or within 30 days.

5.6.2.4. COPD Exacerbations

COPD exacerbations and levels of exacerbation are defined in Section 5.6.3.4. Exacerbations of COPD were recorded in the COPD exacerbation section of the CRF. Any exacerbation of COPD, regardless of level, that fulfilled the Serious Adverse Experience criteria was recorded in the COPD Serious Adverse Experience pages of the CRF.

5.6.2.5. Gastrointestinal Adverse Experiences

Adverse experiences related to the gastrointestinal system (GIAE's) were closely monitored during this study. At the start of the study subjects were instructed to call the Investigator to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting), which caused them concern or interfered with their daily activities (including eating and sleeping). They were reminded of these procedures at each clinic visit. The Investigator had to complete a clinical assessment of the GIAE (s) within 24 hours of occurrence. This assessment included a structured history of the adverse experience including relationship to the time of dosing with study medication and food intake; a physical examination with emphasis on the abdomen; and an assessment of orthostatic changes in heart rate and blood pressure. In addition, laboratory assessments were performed: complete blood count with white cell differential; amylase, electrolytes, blood glucose, and liver function tests; urinalysis including microscopic examination, if indicated; and a faecal occult blood test. If a faecal occult blood test was positive, this was followed up according to

normal clinical practice. After protocol amendment 4, positive faecal occult blood tests found in conjunction with gastrointestinal adverse experiences of concern or melaena were required to be referred to a gastroenterologist for a colonoscopy, irrespective of other identified pathology or causes for gastrointestinal bleeding. The colonoscopy was to include visualisation of the transverse colon, with positive or negative findings reported back to GSK. Biopsies were to be taken if appropriate. Where necessary, additional testing was performed at the discretion of the Investigator according to normal clinical practice.

The Investigator reviewed the results of the initial assessment and arranged further follow-up as appropriate. Any new or worsening symptoms prompted a further follow up assessment visit. All experiences were to be followed to resolution. If the subject experienced symptoms which were severe or persistent and considered by the Investigator to be study-drug related, withdrawal of the subject was considered.

5.6.2.6. Physical Examination

A complete physical examination (including respiratory examination) was performed at 24-week intervals, or at early withdrawal and the Safety Follow-up visit (if abnormal at the previous visit). All significant findings were recorded in the CRF.

5.6.2.7. Vital Signs

Greater than two hours after the subject's last short-acting beta₂-agonist or greater than 12 hours after the last long-acting beta₂-agonist administration, vital signs (blood pressure and heart rate) were measured at every visit. They were recorded after the subject had been sitting for at least 5 minutes.

Orthostatic vital signs were measured at Weeks 24, 48 and then every 48 weeks, at early withdrawal and at visits associated with gastrointestinal adverse experiences. Orthostatic blood pressure and heart rate were obtained after the subject had been supine for five minutes and then after the subject had been sitting up with legs dependent for one minute.

5.6.2.8. Electrocardiogram (ECG)

At least 2 hours after the subject's last short-acting beta₂-agonist or 12 hours after the last long-acting beta₂-agonist administration, a 12-lead ECG was performed at all visits including early withdrawal, and Follow-up (if abnormal at the previous visit). It was performed after the subject had been semisupine for 5 minutes. The ECG machine (Marquette) was supplied by Biomedical Systems, Brussels, Belgium. Each ECG recording was clearly labelled with subject initials, subject identification number, protocol number, centre number and date performed. The ECGs were reviewed by the Investigator for clinically significant abnormalities. ECGs were transferred electronically to a centralised facility (Biomedical Systems, Brussels, Belgium) for data processing. A Board Certified cardiologist at Biomedical Systems performed ECG interpretation.

Particular attention was paid to accurate measurements of QT intervals. The Marquette 12-lead ECG machine determines the median QT interval for each lead. It then

calculates the QT interval as the earliest onset of the Q-wave to the latest offset of the T-wave across all leads. QT values were corrected by applying the Bazett correction factor using the following formula:

$$QTc = UQT / \text{SQRT} (60/VR)$$

(corrected QT = [uncorrected QT] divided by [square root of (60 divided by Ventricular Rate)])

Any QTc values greater than 500msec were manually verified by the over-reading cardiologist.

5.6.2.9. Clinical Laboratory Evaluations

Blood (approximately 20mL) and urine samples for clinical laboratory testing were collected at all visits and at early withdrawal. Samples were taken at the Follow-up Visit, only if abnormalities were observed at the previous visit. A urine pregnancy test was performed at the Follow-up Visit for all women of child-bearing potential.

The following variables were measured:

Haematology:	Haemoglobin concentration, haematocrit, red cell count, white cell count with differential, platelet count.
Clinical chemistry:	Blood urea (reported as blood urea nitrogen), creatinine, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), gamma glutamyl-transferase (GGT), alkaline phosphatase (ALP), total protein, albumin, total bilirubin, sodium, potassium, chloride, glucose, uric acid. Amylase was measured for subjects who had gastrointestinal adverse experiences that were of concern or that interfered with daily activities.
Faeces:	Faecal occult blood tests at Weeks 24, 48 and every 48 weeks thereafter, at early withdrawal, and in subjects who had gastrointestinal adverse experiences of concern.
Urinalysis:	Blood, glucose, protein, ketones.
Pregnancy:	Serum beta-human chorionic gonadotropin (HCG) for women of childbearing potential at 4-week intervals. Urinary beta-HCG for women of childbearing potential at the Follow-up Visit.

Additional laboratory tests were performed where indicated for subjects who reported gastrointestinal adverse experiences which were of concern to them or interfered with their daily activities.

Three faecal occult blood tests on consecutive bowel movements, if possible, were to be performed according to the instructions provided with the faecal occult blood kits. In particular, subjects were not to collect samples during or until 3 days after a menstrual period or while they had bleeding haemorrhoids or blood in the urine. In addition, subjects were to avoid aspirin or other non-steroidal anti-inflammatory drugs for 7 days

prior to and during the test period and to avoid vitamin C in excess of 250 mg per day from all sources, red meat including processed meats and liver, and raw fruits and vegetables for 72 hours prior to and during the test period. When the samples were returned for analysis, the Investigator questioned the subject to determine whether the instructions were followed. Faecal occult blood tests undertaken in association with gastrointestinal adverse events of concern did not follow the strict dietary requirements pre test as these were carried out as soon as possible after gastrointestinal symptoms were reported. These were therefore more open to a higher incidence of false positive results.

A central laboratory, Quest Diagnostics (formerly SmithKline Beecham Clinical Laboratories,) was used for the routine haematological and biochemical assessments in Europe and South Africa. The central laboratory, Dorevitch, was used for analysis of samples from centres in Australia. Urinalysis was initially performed at the site using a dipstick. If abnormalities were found, full microscopy was performed by Quest Diagnostics or Dorevitch.

Clinically significant worsenings in laboratory findings were recorded in the Adverse Experiences section of the CRF and repeated until the values returned to normal. Values outside the reference range, but of no clinical significance, were marked “NCS” by the Investigator on the printed laboratory report sheet.

5.6.3. Efficacy Assessments

The primary objective of this study was to assess the long-term safety and tolerability of SB-207499 and so no primary efficacy measure was defined. The measures of efficacy included:

- Clinic trough pulmonary function tests:
 - Forced expiratory volume in 1 second (FEV_1)
 - Forced expiratory volume in 6 seconds (FEV_6)
 - Forced vital capacity (FVC)
 - Peak expiratory flow rate (PEFR)
 - Forced expiratory flow at 25-75% of vital capacity (FEF_{25-75})
 - Forced expiratory flow at 75% of vital capacity (FEF_{75})
- Dyspnoea assessments (modified Borg scale) at rest and after exercise tolerance test.
- Exercise tolerance test (distance walked during 6-minute walk).
- COPD exacerbation rates.

5.6.3.1. Pulmonary Function Tests

At all visits, except Week 1, pulmonary function tests were performed. Subjects were asked to refrain from using short acting beta₂-agonists, anticholinergic medications and from smoking during the 2-hour period preceding the measurement of pulmonary function tests and from using long acting beta₂-agonists during the 12-hour period

preceding the measurements. Tests were performed at trough (pre-dose) plasma levels of study medication.

FEV₁, FEV₆, FVC, PEF_R, FEF₂₅₋₇₅, and FEF₇₅ were measured according to the BTPS (Body Temperature and Pressure Standard) convention using the spirometer provided for the study (Koko spirometers, PDS). The spirometers were suitable for research purposes, and were calibrated and maintained to acceptable respiratory function laboratory standards.

All pulmonary function tests were performed after the subject had been at rest for at least 10 minutes after an exercise tolerance test. Pulmonary function tests were repeated up to 8 times to obtain three acceptable readings according to ATS guidelines [[American Thoracic Society](#), 1995a]. For each set of three measurements, one FEV₁ had to be within 10% of the highest value recorded.

All sites participating in the extension study used spirometers provided by PDS with software provided by Biomedical Systems, Brussels, Belgium. All pulmonary function tests were performed in accordance with the spirometry manual provided to each site, and the data were transmitted electronically to a centralised facility (Biomedical Systems, Brussels, Belgium). All personnel performing pulmonary function testing for this study were required to have attended a training session run by Biomedical Systems and to be certified by Biomedical Systems before they could perform testing for the feeder study.

The technical quality of the pulmonary function tests was assured by review of any tests falling outside defined limits by a registered pulmonary technician employed at Biomedical Systems.

Data were transferred electronically from Biomedical Systems to the data management facility at Quintiles, Dublin, Ireland.

5.6.3.2. Dyspnoea Assessments (At Rest And After Exercise Tolerance Test)

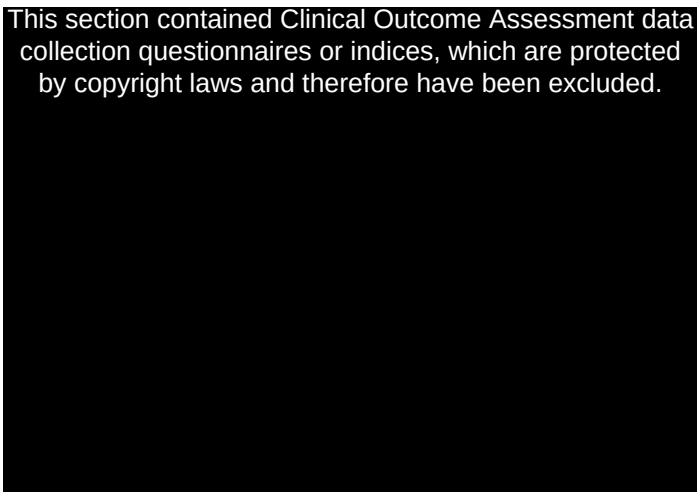
Overall breathlessness at rest was assessed at each visit, except Week 1, early withdrawal, and the final visit, using the modified Borg scale [[Borg](#), 1982]. The subject was asked the following question:

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

Breathlessness following the exercise tolerance test (see Section [5.6.3.3](#)) was assessed at 12-week intervals and at early withdrawal using the modified Borg scale [[Borg](#), 1982]. Immediately after the exercise tolerance test (6-minute walk), the subject was asked the following question:

For each assessment, subjects rated their breathlessness on a scale of 0 to 10, using the following scale.

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.



Investigators showed the scale to subjects when the assessment was made. Responses were not limited to whole numbers.

5.6.3.3. Exercise Tolerance Test

At 12-week intervals i.e., Week 12, 24, 36, and 48 etc., and at early withdrawal, a 6-minute walk test as described by Guyatt and colleagues was used to assess the functional capacity of the subject [Guyatt, 1985; Jones, 1988].

The 6-minute walk was conducted more than 2 hours after the subject's last short-acting beta₂-agonist and more than 12 hours after the last long acting beta₂-agonist administration, and where possible was conducted by the same person to avoid inter-rater variability. The subject was instructed to walk from one end of a course to the other, covering as much ground as they could during 6 minutes. The subject was encouraged to perform during the tests; the supervisor faced the subject every 30 seconds and delivered one of the following encouraging phrases: "You're doing well!" or "Keep up the good work!". At the end of the test, the supervisor called out "Stop" and the distance walked by the subject was measured and recorded on the CRF.

5.6.3.4. COPD Exacerbations

COPD exacerbations, defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy, were recorded throughout the study in a COPD exacerbation section in the CRF. COPD exacerbations were categorised as Level 1, 2, or 3, based on the treatment received by the subject. The levels of exacerbation were defined as follows:

Level 1 Exacerbation: Acute worsening of COPD that is self-managed by the subject at home by increasing usual COPD medications (i.e., the subject does not see a doctor for this episode).

Level 2 Exacerbation: Acute worsening of COPD that requires additional treatment (e.g., a short course of oral steroids, antibiotics, etc.) prescribed by a family physician or

primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3 Exacerbation: Acute worsening of COPD that requires the subject to be admitted to the hospital for treatment.

If the subject had an exacerbation during the study, which lasted more than 2 weeks, the Investigator was to contact GSK regarding the subject's continuation in the study.

5.6.4. Health Outcomes Assessments

Both humanistic and resource utilisation outcomes were included in this study.

5.6.4.1. Humanistic Outcomes

Humanistic outcomes included:

- St George's Respiratory Questionnaire (SGRQ) Total and domain scores.
- Short Form Survey 36 (SF-36).

St George's Respiratory Questionnaire (SGRQ)

The SGRQ was given to the subjects to complete in the clinic at Weeks 0, 12, 24, and every 24 weeks thereafter, prior to all other scheduled procedures. Any subject who withdrew from the study also completed the SGRQ at the time of withdrawal.

The SGRQ is a self-administered questionnaire designed to measure and quantify the impact of chronic respiratory disease on health-related quality of life and well-being [Jones, 1991]. The SGRQ measures the impact of chronic respiratory disease on three domains: symptoms, activity, and impact (on daily life). The first part of the questionnaire ("Symptoms") contains questions that evaluate distress due to respiratory symptoms, including frequency of cough, sputum production, wheeze, breathlessness, and the duration and frequency of attacks of breathlessness or wheeze. The second part has two components, "Activity" and "Impacts". The "Activity" section addresses the effects of disturbance due to mobility and physical activity that cause breathlessness or are limited because of breathlessness. The "Impacts" section covers a range of factors quantifying the psychosocial impact of the disease including influence on employment, being in control of health, panic, stigmatisation, the need for medication, side effects of prescribed therapies, expectations for health, and disturbances of daily life.

A total score was calculated for the questionnaire, and sub-scores were calculated for each of the three component domains. The scoring range for the questionnaire was 0 to 100, with a higher score indicating a poorer level of health. A 4-point difference in score was considered to be clinically meaningful [Jones, 1991].

Short Form Survey 36 (SF-36)

The SF-36 was given to the subjects to complete in the clinic at Week 0 and every 24 weeks thereafter. Any subject who withdrew from the study also completed the SF-36 at the time of withdrawal.

The SF-36 is a general quality-of-life assessment tool used to evaluate the physical, mental, and general health status of subjects. It contains 36 questions/statements and one multi-item scale measuring limitations in physical activities because of health problems, limitations in social activities because of physical or emotional problems, limitations in usual role activities because of physical health problems, pain, general mental health, limitations in usual role activities because of emotional problems, vitality (energy and fatigue), and general health perceptions [Ware, 1992; SF-36 Health Survey, 1993].

The SF-36 was scored using the standard scoring methodology described in the SF-36 reference manual [SF-36 Health Survey, 1993]. The scoring range for the questionnaire was 0 to 100, with a lower score indicating a poorer level of health.

5.6.4.2. Resource Utilisation

Throughout the study, data on the utilisation of medical care as a result of COPD exacerbations were collected and recorded in the CRF. Medical care utilisation included hospitalisation, length of stay in intensive care units, emergency room visits, non-protocol physician office visits, physician office phone contacts for advice on management of an exacerbation, and medications used in the treatment of a COPD exacerbation (antibiotics, oral corticosteroids, beta₂-agonist via nebuliser or injection and oxygen).

Data were collected at each visit on the number of workdays lost as a result of an exacerbation episode.

5.7. Data Quality Assurance

To ensure that study procedures were consistent across all Investigator sites, the protocol, CRF and safety reporting were reviewed with the Investigator and his/her personnel responsible for the conduct of the study by the Company representatives at the Investigator site. Local investigator meetings were held on 21 May 1999 in [REDACTED] Spain, on 6 August 1999 in [REDACTED] Estonia and on 15 July 2002 in [REDACTED] Italy. Adherence to the protocol requirements and verification of data generation accuracy was achieved through monitoring visits to each Investigator site.

The data management functions were performed by Quintiles, Ireland (Quintiles) and managed centrally by GSK R&D.

At the clinical study sites, the Investigator or designee recorded all required subject data in paper CRFs. The completed, original CRFs were returned to GSK where they were first imaged by an onsite vendor, Archive and Access Technology (A&AT) and then tracked into Case Report Form Activity System (CRAMS). Working copies of the CRFs

were made and then sent to Quintiles for data processing. After September 2002 original CRF copies were sent to Quintiles for annotation.

The protocol specific database was originally imported from GSK at study start in Clintrial 3.3 and the data entry screens were tested with dummy data. The Standard Query Logic (SQL) check programmes, as specified in the Data Validation Specifications were programmed; a quality control check was performed and validated using test data. In July 2001, the 040 database was migrated to Clintrial 4.2 by GSK and Clintrial 4.2 metadata and data were re-imported by Quintiles. The Clintrial 4.2 data entry screens were tested using dummy data. The SQL check programmes were run over a percentage of the data pre and post migration and the check output was verified to be identical.

Data values recorded on the CRF were single entered directly in the Clintrial 4.2 database.

Pulmonary function and ECG data were transmitted via Biomedical Systems, Brussels, Belgium and sent to Quintiles.

Laboratory data were sent electronically to Quintiles by two centres (Dorevitch, Australia for Australian subjects and Quest, UK for subjects from all the remaining participating countries).

Pulmonary function, ECG and laboratory data were all transferred electronically in a specified format and loaded directly in to the Clintrial 4.2 database.

Selected variables were coded via the Clintrial 4 standalone autoencoder using standard dictionaries, World Health Organisation Adverse Reaction Terminology (WHOART), World Health Organisation Drug and International Classification of Diseases - Revision 9 (ICD-9).

Computerised data validation was then performed using SQL programmes for both CRF and electronic data. Validation discrepancies, if not covered in accordance with protocol specific Data Validation Specifications and Data Monitoring Specifications provided by GSK, were documented on Data Resolution Query (DRQ) forms. These were sent out to the relevant Investigator for resolution. In such cases, the Investigator was requested to sign and date any explanation or correction. On return, the database and CRF was updated appropriately and the original DRQ stored with the working copy of the CRF.

Additional quality control (QC) was performed in accordance with the protocol specific QC plan. Study start QC was performed on five modules of data. Following migration to Clintrial 4.2, ongoing QC was performed on data for three subjects. 100% QC of critical data was carried out on an ongoing basis and was completed prior to clean data transfer.

Data was sent by Quintiles to GSK via FTP (File Transfer Protocol) server link and was then imported using Oracle import into Clintrial 4.2.

The final clinical report has also been subject to an end-stage quality control review.

5.8. Data Analysis Methods

5.8.1. Timings of Planned Analyses

5.8.1.1. Interim Analyses and Data Monitoring

An interim analysis with a data cut-off date of 15 March 2002 has been performed and reported [[GSK Document Number SB-207499/RSD-1017MT/1](#)]. Since this was a long-term open-label safety study, the interim analysis was performed to monitor the safety of SB-207499.

5.8.1.2. Changes in Conduct of the Study or Planned Analyses

All analyses were detailed in the Reporting and Analysis Plan (RAP). There were no changes in the analysis methods.

5.8.2. Sample Size Considerations

No formal power calculations were performed since this was an open-label study with the primary purpose of evaluating subject safety. It was estimated that approximately 600 subjects would be enrolled at 200 centres in Europe, South Africa and Australia participating in study 042 or study 091.

5.8.3. Analysis Populations

The population for safety analyses included all subjects who had received at least one dose of study medication in study 040.

The population for efficacy analyses included subjects who had received at least one dose of study medication in study 040 and had a baseline assessment from either study 042 or study 091, and at least Day 1 and one post-Day 1 efficacy assessment from study 040.

5.8.4. Treatment Comparisons

The primary comparison of interest was the within group change from the baseline assessment of the feeder study (study 042 and study 091). An additional comparison was a within group change from Visit 1 of study 040 for subjects randomised to placebo in the feeder study. No comparison between the two groups was performed.

5.8.5. Data Handling Conventions

5.8.5.1. Derived and Transformed Data

Smoking History

Pack year smoking history was calculated by dividing the number of cigarettes the subject smokes per day by 20 and then multiplying by the number of years the subject had been smoking.

Derivation of Efficacy Variables for Analysis

For each clinic pulmonary function parameter, three acceptable readings were recorded at each scheduled evaluation. The highest of the three readings was used in the analysis. If more than one set of readings was available for a particular assessment, the later of the two readings was used in the analysis. Pulmonary function tests were performed at all visits in the absence of salbutamol and were performed at trough plasma levels of study medication.

From each set of three efforts, the 'best' pulmonary function parameters were used for analysis. For FEV₁, FVC and PEF_R this was defined as the highest value for each parameter from the three efforts; the values for each parameter did not necessarily come from the same effort. For FEV₆, the value was taken from the effort with the highest FVC. For FEF₇₅ and FEF₂₅₋₇₅, the value was taken from the single effort with the highest summed value of FEV₁ and FVC. For the FEV₁/FVC ratio, both values were taken from the effort with the highest values (highest FEV₁ with the corresponding FVC).

% Predicted FEV₁ was calculated at entry of feeder studies and was defined as:

$$\frac{100 * (\text{Post-bronchodilator FEV}_1)}{\text{Predicted FEV}_1}$$

Predicted FEV₁ values were calculated using the Crapo predicted equations as follows. No race adjustment was made. The equations were pre-programmed in the Koko device.

Females: FEV₁(L) = 0.0342H-0.0255A-1.578

Males: FEV₁(L) = 0.0414H-0.0244A-2.190

H=height in cm, A=age in (whole) years.

In order to maintain constant predicted values, age remained frozen throughout the study and was not incremented if the subject had a birthday during the study.

Reversibility to salbutamol was also calculated at entry to the feeder studies and was defined as:

$$\frac{[(\text{Post - bronchodilator FEV}_1) - (\text{Pre - bronchodilator FEV}_1)] * 100}{\text{Pre - bronchodilator FEV}_1}$$

FEV₁/FVC ratio was also calculated at entry to the feeder studies and defined as:

$$\frac{\text{Pre-bronchodilator FEV}_1}{\text{Pre-bronchodilator FVC}}$$

The maximum pre-bronchodilator FEV₁ and corresponding FVC was used.

On-therapy early withdrawal visits were analysed as part of the LOCF analysis.

For each pulmonary function test (PFT) change from baseline was defined at each visit as:

(PFT at Visit) - (PFT at pre-dose assessment at baseline)

Baseline was defined as the pre-dose evaluation at Visit 3 of the feeder study (either study 042 or study 091). For subjects randomised to placebo in the feeder studies, change from Day 1 was also calculated as the difference between the visit evaluation and the first day of dosing in study 040.

Derivation of Health Outcomes Variables for Analysis

The SGRQ and SF-36 scores were derived according to algorithms provided by the scales' developers. Change from baseline and change from Day 1 were calculated as described for efficacy parameters.

5.8.5.2. Assessment Windows

The date for each visit was defined as the date recorded on the Presentation to Clinic page of the CRF. If this date was not available the date on which the pulmonary function testing was performed was used.

5.8.5.3. Values of Clinical Concern

The sponsor-defined values of potential clinical concern for clinical laboratory tests, vitals signs and ECGs are shown in [Table 3](#), [Table 4](#) and [Table 5](#) respectively.

Table 3 Sponsor-Defined Laboratory Values of Potential Clinical Concern

Parameter	Low Value of Concern	Low	High	High Value of Concern
Haemoglobin	<0.8 x LLN	(0.8 x LLN – 1 x LLN)	(1 x ULN – 1.2 x ULN)	>1.2 x ULN
Haematocrit	<0.8 x LLN	(0.8 x LLN – 1 x LLN)	(1 x ULN – 1.2 x ULN)	>1.2 x ULN
WBC	$\leq 3.0 \times 10^3/\text{mm}^3$	$(3.0 \times 10^3/\text{mm}^3 - 1 \times \text{LLN})$	$(1 \times \text{ULN} - 20.0 \times 10^3/\text{mm}^3)$	$\geq 20.0 \times 10^3/\text{mm}^3$
Neutrophil (total)	<0.8 x LLN	(0.8 x LLN – 1 x LLN)	(1 x ULN – 1.5 x ULN)	>1.5 x ULN
Eosinophil	ND	ND	(1 x ULN – 2 x ULN)	>2 x ULN
Platelet Count	<100 x 10 ⁹ /L	$(100 \times 10^9/\text{L} - 1 \times \text{LLN})$	$(1 \times \text{ULN} - 500 \times 10^9/\text{L})$	>500 x 10 ⁹ /L
AST (SGOT)	ND	ND	(1 x ULN – 2 x ULN)	>2 x ULN
ALT (SGPT)	ND	ND	(1 x ULN – 2 x ULN)	>2 x ULN
GGT	ND	ND	(1 x ULN – 2.5 x ULN)	>2.5 x ULN
Total Bilirubin	ND	ND	(1 x ULN – 1.5 x ULN)	>1.5 x ULN
Alkaline Phosphatase	ND	ND	(1 x ULN – 2 x ULN)	>2.0 x ULN
Creatinine	<0.5 x LLN	(0.5 x LLN – 1 x LLN)	(1 x ULN – 1.5 x ULN)	>1.5 x ULN
BUN (SI Units)	ND	ND	$(1 \times \text{ULN} - 17.85 \text{ mmol/L})$	>17.85 mmol/L
(non SI Units)	ND	ND	$(1 \times \text{ULN} - 50 \text{ mg/dL})$	>50 mg/dL
Urea	ND	ND	$(1 \times \text{ULN} - 17.85 \text{ mmol/L})$	>17.85 mmol/L
Sodium (SI Units)	$\leq 130 \text{ mmol/L}$	$(130 \text{ mmol/L} - 1 \times \text{LLN})$	$(\text{ULN} - 150 \text{ mmol/L})$	$\geq 150 \text{ mmol/L}$
(non-SI Units)	$\leq 130 \text{ mEq/L}$	$(130 \text{ mEq/L} - 1 \times \text{LLN})$	$(\text{ULN} - 150 \text{ mEq/L})$	$\geq 150 \text{ mEq/L}$
Potassium (SI Units)	$\leq 3.0 \text{ mmol/L}$	$(3.0 \text{ mmol/L} - 1 \times \text{LLN})$	$(\text{ULN} - 5.5 \text{ mmol/L})$	$\geq 5.5 \text{ mmol/L}$
(non-SI Units)	$\leq 3.0 \text{ mEq/L}$	$(3.0 \text{ mEq/L} - 1 \times \text{LLN})$	$(\text{ULN} - 5.5 \text{ mEq/L})$	$\geq 5.5 \text{ mEq/L}$
Glucose (fasting/non-fasting)	<2.0 mmol/L	$(2.0 \text{ mmol/L} - 1 \times \text{LLN})$	$(\text{ULN} - 8.0 \text{ mmol/L})$	>8.0 mmol/L
Uric Acid	ND	ND	$(\text{ULN} - 1.4 \times \text{ULN})$	>1.4 x ULN

LLN = Lower Limit of Normal; ULN = Upper Limit of Normal; ND = Not Defined

(x – y) = value >x and ≤y; [x – y] = value ≥x and <y; (x – y) = value >x and <y

Table 4 Vital Sign Values of Potential Clinical Concern

Vital Signs	Low Concern	Low	Reference Range	High	High Concern
Systolic BP (mmHg)	<75	75-89	90-139	140-180	>180
Diastolic BP (mmHg)	<50	50-59	60-89	90-110	>110
Heart rate (bpm)	<50	50-59	60-99	100-120	>120
Orthostatic change ¹ in systolic BP (mmHg)	ND	ND	ND	decrease of 10-19	decrease of ≥ 20
Orthostatic change ¹ in diastolic BP (mmHg)	ND	ND	ND	ND	decrease of ≥ 10
Orthostatic change ¹ in heart rate (bpm)	ND	ND	ND	ND	increase of ≥ 10

ND = not defined

1. Orthostatic change assessed as change between supine for 5 minutes followed by sitting with legs dependent for 1 minute.

Table 5 ECG Values Defined by the Sponsor to be of Potential Clinical Concern

ECG parameter	Low Concern	Low	Reference Range	High	High Concern
QRS interval (msec)	ND	ND	ND	120-199	≥ 200
PR Interval (msec)	ND	ND	ND	200-249	≥ 250
Atrial rate (bpm)	<50	50-59	60-99	100-120	>120
Ventricular rate (bpm)	<50	50-59	60-99	100-120	>120
QTc (msec)	ND	ND	ND	borderline: male: 430-450 female: 450-470	prolonged: male: >450 female: >470
QTc change from baseline (msec)	ND	ND	ND	increase 30-60	increase >60
QT (uncorrected) (msec)	ND	ND	ND	ND	≥ 500

ND = not defined

5.8.6. Study Population

5.8.6.1. Disposition of Subjects

The number of subjects enrolled by each investigator was tabulated. The number of subjects eligible for efficacy and safety analyses was also tabulated.

5.8.6.2. Protocol Deviations

No criteria for exclusion of subjects who deviated from the protocol were defined for this study and no subjects were excluded from the efficacy analyses for deviation from the protocol. Subjects identified as conduct of study deviators were summarised.

5.8.6.3. Demographic and Baseline Characteristics

Descriptive statistics were provided for all demographic and baseline characteristics. These included age, sex, race, smoking history, alcohol intake, COPD duration and pulmonary function parameters.

Prior and current medical conditions and concomitant medications were summarised. Coding was performed as appropriate as described in Section 5.7.

A concomitant medication was defined as any medication used following initial dose of study medication including continuing prior medications. Prior medications were defined as any medication used prior to Visit 1 of study 040 including those that continued into study 040. Post-therapy medications were defined as any medication initiated after the last medication and did not include continuing medications from the active treatment period. Medications initiated on the last day of treatment were classified as post-therapy medications.

5.8.6.4. Treatment Compliance

Compliance at each visit was calculated and defined as:

$$\frac{100 * \text{Number of tablets of study medication consumed}}{2 * \text{Number of days between visits}}$$

where the number days between visits is defined as (Date of current visit - Date of previous visit) and the number of tablets consumed was defined as the number dispensed minus the number returned minus the number lost.

For evening visits an additional half-day was added to the number of days between visits. and one-half day subtracted from the number of days to the next visit.

Overall compliance was also calculated and defined as:

$$100 * \frac{\sum \text{tablets consumed over double-blind period}}{2 * \text{Days of available compliance data on-therapy}}$$

where days of available compliance data on-therapy was defined as the total number of days for which compliance data was available during study 040.

Exposure to study medication was defined without accounting for prior exposure in the feeder studies. Exposure was calculated as:

$$\text{Date of last dose in study 040} - \text{Date of first dose in study 040} + 1$$

An enrolled subject was defined as any subject confirmed to have received open-label study medication in study 040.

Subjects who were lost to follow-up and for whom a first dose date was not available but were confirmed to have received open-label study medication had an assumed exposure of one day.

5.8.7. Safety Evaluations

Evaluation of safety data included all subjects who received at least one dose of study medication. Primary consideration was given to presentation of the safety data without regard to randomised treatment in the feeder study. A secondary presentation of safety data was given by randomised treatment in the feeder study.

5.8.7.1. Adverse Experiences

Adverse experiences were summarised by time to onset, severity, and investigator-reported relationship of the adverse experience to study medication. Gastrointestinal adverse experiences of concern were summarised separately. The proportion of subjects withdrawn due to adverse experiences and due to gastrointestinal adverse experiences of concern was evaluated.

An on-therapy adverse experience was defined as any experience with an onset date on or after the date of initial study 040 dose and up to and including one day after the last dose of study medication in study 040. A post-therapy adverse experience was defined as any experience with an onset date from 2 days after the last dose of study medication.

An adverse experience leading to withdrawal was defined as any on-therapy experience where the “withdrawn” field was checked as “Yes”.

Adverse experiences with missing onset dates were assumed to be on-therapy with an onset on Day 1 of the open-label treatment period. For partial dates, a ‘worst case’ assumption was made: for partial onset dates, the date was assumed to be the first of the month; for partial recovery dates, the date was assumed to be the last day of the month.

Data on serious adverse experiences come from two different databases and have been collected at different time points. Although key data in the databases have been reconciled, minor discrepancies in details of the serious adverse experiences among individual subject narratives and the data source tables and listings may remain. It is considered, however, that these differences, if any, are of a minor nature and do not change the overall significance or understanding of the serious adverse experiences.

5.8.7.2. Clinical Laboratory Tests, Vital Signs and ECGs.

For clinical laboratory tests, vital signs and ECG intervals descriptive statistics were provided at each visit.

For clinical laboratory tests, the percentage of subjects outside the normal limits and with values of sponsor-defined clinical concern was tabulated across all on-therapy visits.

Vital signs of clinical concern, orthostatic vital signs of clinical concern, and ECGs of clinical concern were tabulated in a similar manner. Orthostatic vital signs of clinical concern were summarised for all subjects enrolled and the subgroup of subjects with gastrointestinal adverse experiences of concern. In addition ECG abnormalities were summarised using SNOMED (Systematised Nomenclature of Human (and Veterinary) Medicine) terminology.

The proportion of subjects with positive faecal occult bloods on-therapy was tabulated for all enrolled subjects and the subgroup of subjects with gastrointestinal adverse experiences of concern.

Gastrointestinal adverse events of concern were explored graphically.

5.8.8. Efficacy Analyses

No primary efficacy measure was defined for this open-label safety study. Efficacy evaluations included:

- Clinic trough FEV₁, FEV₆, FVC, FEF₂₅₋₇₅, FEF₇₅, and PEFR
- Overall and post-exercise breathlessness (Borg scale).
- Exercise tolerance test (distance walked during 6-minute walk).
- COPD exacerbation rates.

The primary comparison of interest was the within group change from the baseline assessment of the feeder study (study 042 or study 091). An additional comparison was a within group change from Visit 1 of study 040 for subjects randomised to placebo in the feeder studies. No comparison between the two groups was performed.

For efficacy analyses, data from the feeder studies 042 and 091 were included in the tables of changes from baseline. For both studies, Week 24 data was considered the end of the double-blind phase of these two studies. In study 091, the final two weeks of treatment (up to Week 26) were considered as run-out phase. These data were not included in any change from baseline tables or change from Day 1 tables.

For changes from Visit 1 in study 040, data from Week 24 in study 042 and from Week 26 in study 091 were used as the Visit 1 data for study 040.

For continuous efficacy endpoints, descriptive statistics (including mean, median, range, standard deviation (sd) and 95% confidence intervals (CI) were provided for the change from baseline at each scheduled study visit. No statistical hypothesis testing was performed.

Annualised rates for COPD exacerbations were estimated using a Poisson regression model.

Description of efficacy variables were given by randomised treatment group in the feeder studies.

5.8.9. Health Outcomes Analyses

The planned health outcomes evaluations were:

- Total and subscale scores of the SGRQ.
- SF-36.
- Health economic measures (days off work, healthcare utilisation).

For continuous endpoints, descriptive statistics (including mean, median, range, standard deviation (sd) and 95% confidence intervals (CI) were provided for the change from baseline at each scheduled study visit. No statistical hypothesis testing was performed.

Annualised rates for resource utilisation were estimated using a Poisson regression model.

6. STUDY POPULATION RESULTS

6.1. Disposition of Subjects

6.1.1. Number and Distribution of Subjects

The study started on 14 June 1999 and finished on 19 September 2002.

The number of subjects enrolled into the study and the number eligible for the efficacy and safety analyses are tabulated in total and by prior treatment in Section 13, [Table 13.1A](#). A total of 723 subjects was enrolled in the study and took study medication. Subject disposition is summarised in [Table 6](#).

Table 6 Subject Disposition

Disposition	Prior Placebo ¹ n (%)	Prior SB-207499 15 mg bd ¹ n (%)	Total n (%)
Enrolled into extension study	243	480	723
Efficacy analysis	232 (95.5%)	469 (97.7%)	701 (97.0%)
Withdrawn from extension study	104 (42.8%)	192 (40.0%)	296 (40.9%)
Completed extension study	139 (57.2%)	288 (60.0%)	427 (59.1%)
Safety analysis	243 (100%)	480 (100%)	723 (100%)

Data Source: Section 13, [Table 13.1A](#), [Table 13.3](#)

1. Treatment received during study 042 or study 091.

The study was conducted at a total of 130 centres in the 10 countries (Australia, Belgium, Finland, France, Germany, Netherlands, Norway, South Africa, Spain and United Kingdom). The distribution of subjects by centre is shown in Section 13, [Table 13.1B](#). The highest recruiting countries were Spain (236 subjects), Germany (135 subjects) and France (134 subjects). The number of subjects recruited by each centre ranged from 1 to 33.

The number of subjects assessed at each study visit is shown in Section 13, [Table 13.2](#). At the time of study completion, there were 623 subjects (86.2%) who had completed Visit 9 (24 weeks) in study 040, 568 (78.6%) who had completed Visit 16 (52 weeks), 449 subjects (62.1%) who had completed Visit 30 (108 weeks) and 303 (41.9%) who had completed Visit 36 (132 weeks). A total of 142 subjects (19.6%) completed Visit 37 (136 weeks) and 608 subjects (84.1%) completed a safety follow-up visit.

6.1.2. Withdrawal Reasons

Reasons for withdrawal from study 040 are shown in Section 13, [Table 13.3](#) and summarised in [Table 7](#). In total, 296 subjects (40.9%) were withdrawn from the study and 427 (59.1%) were recorded as having completed the study. The 20 subjects enrolled in Norway were not able to continue in the study beyond 96 weeks, as extension to the protocol (protocol amendment 3) was not approved in that country. In addition, 5

subjects in Germany were also unable to continue treatment beyond 96 weeks since ethical approval to continue was not available for some centres at the time of the study visits.

Table 7 Number (%) of Subjects Withdrawn From The Study by Reason For Withdrawal

Reason for Withdrawal	Prior Placebo (N =243)	Prior SB-207499 15 mg bd (N =480)	Total (N = 723)
Adverse experience ¹	55 (22.6%)	80 (16.7%)	135 (18.7%)
COPD exacerbation	5 (2.1%)	7 (1.5%)	12 (1.7%)
Insufficient therapeutic effect	1 (0.4%)	7 (1.5%)	8 (1.1%)
Protocol deviation (including non-compliance)	5 (2.1%)	6 (1.3%)	11 (1.5%)
Lost to follow-up	1 (0.4%)	9 (1.9%)	10 (1.4%)
Other ²	42 (17.3%)	90 (18.8%)	132 (18.3%)
Total withdrawn	104 (42.8%)	192 (40.0%)	296 (40.9%)
Total completed ³	139 (57.2%)	288 (60.0%)	427 (59.1%)

Data Source: Section 13, [Table 13.3](#)

1. Adverse experience includes subjects whose adverse experience started during the current study or within the previous feeder studies. Figures also include subjects withdrawn due to COPD exacerbations.
2. Other reasons include: subject withdrew consent/no longer wanted to take part, Investigator wished to stop the study/centre closed, Investigator believed study had ended, concurrent medical condition/planned surgery.
3. Includes subjects in Norway and Germany where no approval was available for longer-term treatment.

Adverse experiences and “other” reasons were the most common reason for subject withdrawal. One hundred and thirty-five subjects (18.7%) withdrew due to adverse experiences and 132 (18.3%) withdrew due to “other” reasons.

Overall, slightly more subjects in the prior placebo treatment group (42.8%) withdrew from study 040 compared with the group comprising subjects previously treated with SB-207499 (40.0%). This was primarily due to a greater number of withdrawals due to adverse experiences in the prior placebo group (22.6% versus 16.7%), for whom this was the first exposure to SB-207499, as compared with the prior SB-207499 group who had previously received SB-207499 for 24 - 26 weeks in studies 042 and 091.

The cumulative percentage (estimated using the Kaplan-Meier product limit) of subjects withdrawn over time, by reason for withdrawal, is presented in Section 13, [Table 13.4](#) and summarised in [Table 8](#). There were slightly more withdrawals due to adverse experiences in the early part of the study for subjects who had previously received placebo than for those who had previously received SB-207499.

Table 8 Percentage of Subjects Withdrawn Due to Adverse Experiences by Time of Withdrawal and Prior Treatment Group

Time¹ (days)	Prior Placebo (N =243)	Prior SB-207499 15 mg bd (N =480)
≤ 7	2.5%	1.9%
≤ 14	5.8%	2.1%
≤ 28	8.3%	2.9%
≤ 56	9.5%	4.2%
≤ 84	10.4%	4.4%
≤ 168	13.4%	5.7%
≤ 336	14.8%	8.2%
≤ 504	16.3%	10.6%
≤ 672	18.8%	13.6%
≤ 840	21.5%	15.8%
≤ 1008	25.2%	18.4%
≤ 1176	32.0%	22.1%

Data source: Section 13, [Table 13.4](#)

1. The number of days is calculated relative to Day 1 of study 040

Percentages are cumulative. Kaplan Meier analysis

6.2. Protocol Deviations

No criteria for exclusion of protocol violators were defined for this study. Subjects identified as conduct of study deviators are summarised in Section 13, [Table 13.5](#); however, their data were not excluded from the efficacy analysis. A high proportion of subjects deviated from the protocol at some time during their participation (89.2%), with the most common reason involving not returning for a scheduled study visit within the protocol-defined visit window (85.6%). A total of 208 subjects (28.8%) had not withheld beta₂-agonists or anticholinergic agents for the specified time period at one or more visits and 76 subjects (10.5%) had entered this study at a time other than the final therapy visit date of the feeder studies. Forty-one subjects (5.7%) had used aminophylline and/or theophylline at some point during the extension study. Other deviations were seen in less than 4% of subjects. The overall high percentage of conduct of study deviators is not unexpected due to the nature and length of this continuation study.

6.3. Populations Analysed

The Safety Population comprised 723 subjects and included all subjects who had received at least one dose of study medication in study 040. This population was used for all safety tabulations and analyses. The Efficacy Population, used for all efficacy analyses, comprised 701 subjects. To be included in this population, subjects were required to have: a baseline assessment from either study 042 or study 091; received at least one dose of study medication; and at least a Day 1 and one post-Day 1 assessment in study 040.

6.4. Demographic and Other Baseline Characteristics

6.4.1. Demographic Characteristics

The demographic characteristics of the subjects enrolled into study 040, based on their entry into study 042 or study 091, are shown in Section 13, [Table 13.6](#). Overall, 84.2% of the subjects were male, 98.5% of the subjects were White and the mean age was 62.9 years. The demographic characteristics of the study population were comparable to those of prior COPD studies conducted in subjects with moderate to severe COPD.

Overall, there were no remarkable differences in the demographic characteristics between the two prior treatment groups as shown in [Table 9](#).

Table 9 Demographic Characteristics (at Entry to Studies 042/091)

Demographic Characteristics	Prior Placebo (N =243)		Prior SB-207499 15 mg bd (N =480)		Total (N =723)	
Sex						
Female [n (%)]	38	(15.6%)	76	(15.8%)	114	(15.8%)
Male [n (%)]	205	(84.4%)	404	(84.2%)	609	(84.2%)
Race						
White [n (%)]	238	(97.9%)	474	(98.8%)	712	(98.5%)
Oriental [n (%)]	5	(2.1%)	5	(1.0%)	10	(1.4%)
Other [n (%)]	0		1	(0.2%)	1	(0.1%)
Age						
> 65 years [n (%)]	107	(44.0%)	208	(43.3%)	315	(43.6%)
Mean (sd) [years]	63.3 (9.1)		62.6 (8.9)		62.9 (9.0)	
Range [years]	39 - 84		39 - 82		39 - 84	

Data Source: Section 13, [Table 13.6](#).

6.4.2. Baseline Characteristics

The baseline characteristics (smoking history, alcohol intake, COPD duration, pulmonary function parameters and % predicted TLCO) of the subjects enrolled into study 040, at entry into studies 042 and 091, are shown in Section 13, [Table 13.7](#) and [Table 13.8](#).

The subjects had a mean smoking history of 44.4 pack years. Current smokers made up 43.4% of the study population, and they smoked an average of 17.8 cigarettes per day at baseline. The mean duration of the subjects' COPD was 8.7 years.

Overall, there were no differences between the two treatment groups with regards to smoking history, alcohol intake, or COPD duration as shown in [Table 10](#).

Table 10 Smoking History, Alcohol Intake, and Duration of COPD (at Entry into Studies 042/091)

Baseline Characteristics		Prior Placebo (N=243)	Prior SB-207499 15 mg bd (N=480)	Total (N=723)
Smoking history				
Current smoker	n (%)	100 (41.2%)	214 (44.6%)	314 (43.4%)
Past-smoker	n (%)	143 (58.8%)	266 (55.4%)	409 (56.6%)
		n=243	n=479	n=722
Pack years	Mean (sd)	43.7 (22.2)	44.8 (23.0)	44.4 (22.7)
	Range	10 - 150	10 - 153	10 - 153
Cigarettes per day		n=100	n=214	n=314
	Mean (sd)	17.5 (11.5)	18.0 (10.5)	17.8 (10.8)
	Range	2 - 60	1 - 40	1 - 60
Alcohol intake (units/week)		n=242	n=478	n=720
	Mean (sd)	6.5 (9.6)	6.2 (9.2)	6.3 (9.3)
	Range	0 - 56	0 - 70	0 - 70
COPD duration (years)		n=242	n=479	n=721
	Mean (sd)	8.5 (8.4)	8.7 (8.4)	8.7 (8.4)
	Range	0 - 44	0 - 55	0 - 55

Data Source: Section 13, [Table 13.8](#)

Details of subjects' smoking status during the study are presented in Section 13, [Table 13.12](#). Throughout the study there were only relatively small changes in smoking status, i.e. non-smokers who had become smokers and vice versa. In total 128 (18%) of patients changed smoking status (41[17%] former placebo and 87[18%] former cilomilast patients). In general, the proportions of subjects who stopped smoking exceed the proportions who started smoking during the study.

Baseline pulmonary function variables are shown in Section 13, [Table 13.7](#) and are summarised in [Table 11](#).

Table 11 Pulmonary Function Parameters and % Predicted TLCO (at Entry to Studies 042/091)

Pulmonary Function Variable		Prior Placebo (N=243)	Prior SB-207499 15 mg bd (N=480)	Total (N=723)
FEV ₁ , L ¹	Mean (sd)	1.50 (0.44)	1.53 (0.45)	1.52 (0.44)
	Range	0.63 - 3.46	0.58 - 3.24	0.58 - 3.46
% Predicted FEV ₁ ²	Mean (sd)	49.4% (11.2)	50.1% (11.3)	49.8% (11.3)
	Range	28.3 - 78.6%	23.1 - 88.2%	23.1 - 88.2%
% Reversibility ³	Mean (sd)	4.9% (8.6)	4.8% (8.7)	4.8% (8.7)
	Range	-25.8 - 54.2	-37.4 - 35.0	-37.4 - 54.2
FVC, L ¹	Mean (sd)	2.88 (0.80)	2.87 (0.78)	2.87 (0.78)
	Range	1.47 - 6.04	1.07 - 5.72	1.07 - 6.04
FEV ₁ /FVC	Mean (sd)	0.54 (0.10)	0.55 (0.10)	0.55 (0.10)
	Range	0.30 - 0.77	0.25 - 0.82	0.25 - 0.82
% Predicted TLCO	n	228	456	684
	Mean (sd)	70.3% (26.4)	69.4% (26.4)	69.7% (26.4)
	Range	20.5 - 186.2%	20.9 - 185.6%	20.5 - 186.2%

Data Source: Section 13, [Table 13.7](#)

1. Reported pre-salbutamol.

2. Reported post-salbutamol inhalation.

3. Calculated as percentage of pre-salbutamol value.

Note: Results are from the Screening Visit of study 042 or study 091.

At entry into study 042 and 091, mean pre-salbutamol FEV₁ was 1.52 L and mean post-salbutamol FEV₁, as a percentage of predicted normal was 49.8%. The pre-salbutamol FEV₁/FVC ratio was 0.55. Reversibility to salbutamol was low, being 4.8%. Baseline pulmonary function tests were indicative of a subject population with moderate COPD although there was wide variation. There was little difference between the two prior treatment groups in terms of baseline lung function.

6.4.3. Other Current Medical Conditions

A summary of prior medical conditions at entry into study 042 or study 091 is provided in Section 13, [Table 13.9A](#). There were 539 (74.6%) subjects with prior medical conditions at Screening to these studies with 296 subjects (40.9%) reporting prior surgical operations. The most common conditions (apart from surgical procedures) were tuberculosis (8.9%) and pneumonia (8.3%, including viral, bacterial and other pneumonia).

Current conditions at entry to study 042 and study 091 are shown in Section 13, [Table 13.9B](#) and the most commonly occurring (≥5% of all subjects) are summarised in [Table 12](#).

Table 12 **Number (%) of Subjects with the Most Common Current Medical Conditions at Entry into Studies 042 and 091 (≥5% of All Subjects)**

Current/Active Medical Condition	Prior SB-207499		Total (N = 723)
	Prior Placebo (N = 243)	15 mg bd (N = 480)	
Total¹	243 (100%)	480 (100%)	723 (100%)
Obstructive lung disease	243 (100%)	480 (100%)	723 (100%)
Hypertension	61 (25.1%)	117 (24.4%)	178 (24.6%)
Chronic bronchitis	26 (10.7%)	49 (10.2%)	75 (10.4%)
Cholesterol/triglyceride elevated	30 (12.3%)	33 (6.9%)	63 (8.7%)
Osteoarthritis	25 (10.3%)	34 (7.1%)	59 (8.2%)
Emphysema	22 (9.1%)	36 (7.5%)	58 (8.0%)
Diabetes mellitus	15 (6.2%)	34 (7.1%)	49 (6.8%)
Ischaemic heart disease	18 (7.4%)	27 (5.6%)	45 (6.2%)
Prostate disorder	14 (5.8%)	24 (5.0%)	38 (5.3%)
Spondylosis	11 (4.5%)	26 (5.4%)	37 (5.1%)
Tobacco use ²	10 (4.1%)	27 (5.6%)	37 (5.1%)

Data Source: Section 13, [Table 13.9B](#)

1. Total represents the total number of subjects with an active condition.
2. Tobacco use was a locally applied term used by a limited number of investigators to refer to current or former nicotine addiction.

The most commonly occurring current condition (excluding COPD) was hypertension (24.6% of subjects). There were no major differences between the treatment groups.

6.4.4. Previous Medications

Prior to the study, concomitant medications had been used by 685 subjects (94.7%). These are summarised in Section 13, [Table 13.10A](#). Salbutamol, used by 610 subjects (84.4%), and ipratropium bromide, used by 273 subjects (37.8%) were the most commonly used medications. In general, no marked differences were observed in the frequency or type of prior medications received by either of the two prior treatment groups.

6.4.5. Concomitant Medications

Details of concomitant medications are provided in Section 13, [Table 13.10B](#) and [Table 13.10E](#). The latter table was required to collapse multiple terms for single medications which resulted in underestimated some categories of concomitant medication use. The medications presented in tabular form below are derived from [Table 13.10E](#). Concomitant medications were those ongoing at the end of study 042 or study 091 or started during study 040 and included both medications that were used consistently during study 040 and those that were used as short courses only. The most commonly received concomitant medications (used by ≥10% of all subjects) are shown in [Table 13](#).

Table 13 Number (%) of Subjects Receiving the Most Common Concomitant Medications ($\geq 10\%$ of All Subjects)

Concomitant Medication	Prior Placebo (N = 243)	Prior SB-207499	Total (N = 723)
		15 mg bd (N = 480)	
Total¹	243 (100%)	479 (99.8%)	722 (99.9%)
Salbutamol	228 (93.8%)	442 (92.1)	670 (92.7%)
Ipratropium bromide	117 (48.1%)	228 (47.5%)	345 (47.7%)
Paracetamol	81 (33.3%)	175 (36.5%)	256 (35.4%)
Amoxycillin	82 (33.7%)	168 (35.0%)	250 (34.6%)
Clavulanic acid	49 (20.2%)	110 (22.9%)	159 (22.0%)
Acetylcysteine	47 (19.3%)	91 (19.0%)	138 (19.1%)
Acetylsalicylic acid	40 (16.5%)	83 (17.3%)	123 (17.0%)
Influenza virus vaccine polyvalent	47 (19.3%)	76 (15.8%)	123 (17.0%)
Salmeterol	42 (17.3%)	80 (16.7%)	122 (16.9%)
Formoterol	40 (16.5%)	74 (15.4%)	114 (15.8%)
Methylprednisolone	31 (12.8%)	69 (14.4%)	100 (13.8%)
Prednisolone	34 (14.0%)	65 (13.5%)	99 (13.7%)
Omeprazole	29 (11.9%)	67 (14.0%)	96 (13.3%)
Azithromycin	37 (15.2%)	54 (11.3%)	91 (12.6%)
Budesonide	36 (14.8%)	52 (10.8%)	88 (12.2%)
Ciprofloxacin	30 (12.3%)	54 (11.3%)	84 (11.6%)
Prednisone	28 (11.5%)	55 (11.5%)	83 (11.5%)
Fluticasone propionate	27 (11.1%)	55 (11.5%)	82 (11.3%)
Cefuroxime	24 (9.9%)	52 (10.8%)	76 (10.5%)
Ranitidine	27 (11.1%)	48 (10.0%)	75 (10.4%)
Clarithromycin	21 (8.6%)	51 (10.6%)	72 (10.0%)

Data Source: Section 13, [Table 13.10E](#)

1. Total represents total number of subjects receiving concomitant medication.
2. Total numbers may be underestimated for some compounds as usage may be detailed under more than one salt.

During study 040, concomitant medications were taken by 722 subjects (99.9%). Overall, the most commonly received concomitant medications were salbutamol (92.7%), ipratropium bromide (47.7%) and paracetamol (35.4%). In general, no marked differences were observed in the frequency or type of concomitant medications received by either of the two prior treatment groups. The medications used were those that might be expected of an elderly population with obstructive lung disease.

Concomitant inhaled long acting beta₂-agonists included formoterol (114 subjects, 15.8%) and salmeterol (122 subjects, 16.9%). Concomitant inhaled corticosteroids were used by 27.8% of subjects (Section 13, [Table 13.13A](#)) and included fluticasone propionate (11.3%), budesonide (12.2%), beclomethasone (3.9%), triamcinolone acetonide (2.6%), mometasone (1.1%) and flunisolide (0.4%). These figures include all usage of these compounds, including usage as part of a combination product with other drug classes.

Medications used to treat COPD exacerbations are shown in Section 13, [Table 13.10C](#). Overall 468 subjects (64.7%) used medications to treat an exacerbation. In general, antibiotics and oral corticosteroids were the medications used most often to treat exacerbations, although acetylcysteine was used by 96 subjects (13.3%) and paracetamol was used by 80 subjects (11.1%). The most commonly used medication was amoxycillin which was used by 173 (23.9%) of subjects. Prednisolone was used by 89 subjects (12.3%), prednisone by 72 (10.0%) and methylprednisolone by 67 (9.3%). A summary of corticosteroids administered orally to treat exacerbations is provided in Section 13, [Table 13.13B](#). Overall, 209 subjects (28.9%) used oral corticosteroids to treat exacerbations. Usage of medications to treat exacerbations was generally similar for the two prior treatment groups.

6.5. Treatment Compliance

Subjects were considered to be compliant with study medication if they had taken between 80% and 120%, inclusive, of the intended regimen in study 040. Subjects were to be withdrawn from the study if study medication compliance at two consecutive visits was not $\geq 80\%$ and $\leq 120\%$. If a subject was withdrawn, compliance was assessed up to the date of cessation of study medication.

The number and percentage of subjects who were compliant for each period of the study are shown in Section 13, [Table 13.11A](#), and the mean and median compliance for each study period are shown in Section 13, [Table 13.11B](#). Compliance was good throughout the study, with the mean percentage compliance at the different study periods ranging from 93.5% (week 1) to 100.3% (week 140). Over the whole study period, the mean compliance was 95.0% and the number of subjects considered to be compliant with study medication was 683 (94.6%). Overall, more subjects in the group treated with SB-207499 in study 042 and study 091 were compliant compared with the prior placebo treatment group (96.2% versus 91.4% respectively). Compliance is summarised in [Table 14](#).

Table 14 Overall Compliance with Study Medication (Number and % of Subjects)

Overall Compliance	Prior Placebo (N = 243)	Prior SB-207499	Total (N = 722)
		15 mg bd (N = 479)	
< 80%	21 (8.6%)	18 (3.8%)	39 (5.4%)
80 – 120	222 (91.4%)	461 (96.2%)	683 (94.6%)
> 120	0	0	0
Mean (sd) compliance	94.4% (12.1)	95.3% (9.8)	95.0% (10.6)
Range	20.0 – 106.8%	17.9 - 107.1%	17.9 – 107.1%

Data Source: Section 13, [Table 13.11A](#) and [Table 13.11B](#)

7. SAFETY RESULTS

7.1. Extent of Exposure

The extent of exposure to study medication is described in Section 15, [Table 15.1A](#) and [Table 15.1B](#). A total of 31 subjects (4.3%) received ≤ 14 days of treatment. Overall, there were 625 subjects (86.4%) with ≥ 169 days (approximately 6 months) of treatment, 573 subjects (79.3%) with ≥ 1 year of treatment, 462 subjects (63.9%) with ≥ 2 years of treatment and 44 subjects (6.1%) with ≥ 3 years of treatment at the end of the study (19 September 2002).

The mean duration of exposure to study medication during study 040 was 744 days. Duration of exposure is summarised in [Table 15](#).

Table 15 **Duration of Exposure**

Duration of Exposure	Prior SB-207499		Total (N = 723)
	Prior Placebo (N = 243)	15 mg bd (N = 480)	
Mean (sd)	707.8 (398.1)	762.3 (344.8)	744.0 (364.2)
Median	910	923	917
Range	1 – 1178	1 – 1149	1 – 1178

Data Source: Section 15, [Table 15.1B](#)

Calculation of exposure: (Date of last dose of 040 study medication – Date of first dose of 040 study medication) + 1.

7.2. Adverse Experiences (AEs)

7.2.1. All Adverse Experiences

The incidences of all adverse experiences which occurred while subjects were on therapy are presented by frequency of occurrence in Section 15, [Table 15.2A](#) and classified by body system in Section 15, [Table 15.2B](#).

In total, 677 subjects (93.6%) reported at least one on-therapy adverse experience. Adverse experiences were most frequently reported in the respiratory system (by 539 subjects, 74.6%), gastrointestinal system (336 subjects, 46.5%) and for the body as a whole (217 subjects, 30.0%). The incidence of adverse experiences in the gastrointestinal body system was higher for subjects who had received prior treatment with placebo than for subject who had received prior SB-207499 treatment (55.1% compared with 42.1%). The incidence of experiences for other body systems was similar for the two prior treatment groups.

The most frequently reported adverse experience was chronic obstructive airways disease (i.e. COPD exacerbation) which occurred in 494 subjects (68.3%). The number (%) of subjects with the most frequently reported on-therapy adverse experiences ($\geq 5\%$ subjects in total) is summarised in [Table 16](#).

Table 16 Number (%) of Subjects with the Most Frequently Reported Adverse Experiences (≥5% Subjects in Total Group)

Adverse Experience (Preferred Term)	Prior SB-207499		Total (N = 723)
	Prior Placebo (N = 243)	15 mg bd (N = 480)	
Total¹	231 (95.1%)	446 (92.9%)	677 (93.6%)
Chronic obstructive airways disease	160 (65.8%)	334 (69.6%)	494 (68.3%)
Abdominal pain	52 (21.4%)	66 (13.8%)	118 (16.3%)
Diarrhoea	47 (19.3%)	55 (11.5%)	102 (14.1%)
Injury	28 (11.5%)	67 (14.0%)	95 (13.1%)
Back pain	24 (9.9%)	58 (12.1%)	82 (11.3%)
Headache	33 (13.6%)	47 (9.8%)	80 (11.1%)
Rhinitis	31 (12.8%)	46 (9.6%)	77 (10.7%)
Upper respiratory tract infection	20 (8.2%)	53 (11.0%)	73 (10.1%)
Nausea	34 (14.0%)	37 (7.7%)	71 (9.8%)
Dyspepsia	32 (13.2%)	35 (7.3%)	67 (9.3%)
Viral infection	21 (8.6%)	40 (8.3%)	61 (8.4%)
Pharyngitis	15 (6.2%)	43 (9.0%)	58 (8.0%)
Arthralgia	20 (8.2%)	33 (6.9%)	53 (7.3%)
Coughing	13 (5.3%)	32 (6.7%)	45 (6.2%)
Hypertension	11 (4.5%)	34 (7.1%)	45 (6.2%)
Chest Pain	15 (6.2%)	29 (6.0%)	44 (6.1%)
Respiratory disorder	12 (4.9%)	29 (6.0%)	41 (5.7%)
Hyperglycaemia	9 (3.7%)	28 (5.8%)	37 (5.1%)
Vomiting	15 (6.2%)	22 (4.6%)	37 (5.1%)

Data Source: Section 15, [Table 15.2A](#)

1. Total represents total number of subjects reporting at least one adverse experience.

Chronic obstructive airways disease occurred at a slightly higher frequency in subjects who had previously taken SB-207499 in studies 042 and 091, whereas gastrointestinal experiences (abdominal pain, diarrhoea, nausea, dyspepsia and vomiting) and headaches occurred more frequently in subjects who had previously taken placebo.

7.2.2. Adverse Experiences by Relationship to Study Medication

The incidence of adverse experiences tabulated by relationship to study medication is shown in Section 15, [Table 15.3](#). A total of 196 subjects (27.1%) reported adverse experiences that were considered by the Investigator to be study drug related (suspected or probably related to treatment). The incidence of drug-related experiences was higher in subjects who had previously received placebo (37.4%) than in subjects who had previously received SB-207499 (21.9%). Adverse experiences of the gastrointestinal system were most frequently reported as being drug-related. A total of 145 subjects (20.1%) reported gastrointestinal experiences that were considered to be drug-related. The number (%) of subjects with the most frequently reported on-therapy adverse experiences, reported by the Investigator as suspected or probably related to study medication in ≥1% subjects in total, is summarised in [Table 17](#).

Table 17 Number (%) of Subjects with the Most Frequently Recorded Adverse Experiences Considered Related to Study Medication ($\geq 1\%$ Subjects in Total Group)

Drug-Related ¹ Adverse Experience (Preferred Term)	Prior Placebo (N = 243)	Prior SB-207499	
		15 mg bd (N = 480)	Total (N = 723)
Total²	91 (37.4%)	105 (21.9%)	196 (27.1%)
Abdominal pain	35 (14.4%)	26 (5.4%)	61 (8.4%)
Diarrhoea	24 (9.9%)	22 (4.6%)	46 (6.4%)
Nausea	22 (9.1%)	14 (2.9%)	36 (5.0%)
Dyspepsia	17 (7.0%)	12 (2.5%)	29 (4.0%)
Headache	13 (5.3%)	6 (1.3%)	19 (2.6%)
Vomiting	12 (4.9%)	3 (0.6%)	15 (2.1%)
Chronic obstructive airways disease	6 (2.5%)	7 (1.5%)	13 (1.8%)
Dizziness	6 (2.5%)	4 (0.8%)	10 (1.4%)

Data Source: Section 15, [Table 15.3](#)

1. Relationships considered “suspected” or “probable” are included in the “related” category.
2. Total represents total number of subjects reporting at least one drug-related adverse experience

All of the most commonly occurring adverse experiences considered by the Investigator to be suspected or probably related to study medication were reported with a higher frequency by subjects who had received prior placebo treatment than by those who had received prior treatment with SB-207499.

7.2.3. Adverse Experiences by Intensity

On-therapy adverse experiences are summarised by Investigator-determined maximum intensity in Section 15, [Table 15.4](#). The percentages of subjects who experienced mild, moderate and severe adverse experiences were comparable between the two prior treatment groups.

Overall, 379 subjects (52.4%) had adverse experiences that were regarded by the Investigator to be of moderate intensity. Severe adverse experiences were experienced by 196 subjects (27.1%). These data are summarised in [Table 18](#).

Table 18 Number (%) of Subjects With On-Therapy Adverse Experiences by Maximum Intensity

Intensity ¹	Prior Placebo (N = 243)	Prior SB-207499	
		15 mg bd (N = 480)	Total (N = 723)
Total²	231 (95.1%)	446 (92.9%)	677 (93.6%)
Mild	36 (14.8%)	66 (13.8%)	102 (14.1%)
Moderate	129 (53.1%)	250 (52.1%)	379 (52.4%)
Severe	66 (27.2%)	130 (27.1%)	196 (27.1%)

Data Source: Section 15, [Table 15.4](#)

1. Maximum intensity is used for each adverse experience for each subject.
2. Total represents total number of subjects reporting at least one adverse experience.

The severe adverse experiences reported by $\geq 1\%$ subjects in total are shown in [Table 19](#). Chronic obstructive airways disease (68 subjects, 9.4%) was the most commonly occurring adverse experience considered to be severe.

Table 19 Number (%) Subjects Reporting Most Common Severe Adverse Experiences ($\geq 1\%$ Subjects in Total Group)

Severe Adverse Experience (Preferred Term)	Prior Placebo (N = 243)	Prior SB-207499	Total (N = 723)
		15 mg bd (N = 480)	
Chronic obstructive airways disease	25 (10.3%)	43 (9.0%)	68 (9.4%)
Pneumonia ¹	3 (1.2%)	11 (2.3%)	14 (1.9%)
Injury	1 (0.4%)	11 (2.3%)	12 (1.7%)
Pulmonary carcinoma	2 (0.8%)	7 (1.5%)	9 (1.2%)
Abdominal pain	4 (1.6%)	4 (0.8%)	8 (1.1%)

Data Source: Section 15, [Table 15.4](#)

1. Includes lobar pneumonia.

7.2.4. Adverse Experiences by Time of First Occurrence

The most frequently reported adverse experiences in each prior treatment group occurring on-therapy by time of first occurrence are summarised in Section 15, [Table 15.5](#). The time of first occurrence of the most frequently reported adverse experiences (reported by $\geq 10\%$ of subjects in total) are shown in [Table 20](#). This summarises the incidences of events up to Day 420 (approximately the first year of the study).

Table 20 Number (%) of Subjects with the Most Frequently Reported Adverse Experiences by Time of First Occurrence

Adverse Experience	N ¹	Time of Initial Onset (Days)											
		1	2-7	8-14	15-28	29-56	57-84	85-112	113-140	141-168	169-252	253-336	337-420
Prior Placebo		n=243	n=242	n=237	n=227	n=220	n=213	n=207	n=200	n=196	n=194	n=187	n=184
	231	23	78	45	52	55	52	47	46	44	76	68	59
Total²	(95.1%)	(9.5%)	(32.2%)	(19.0%)	(22.9%)	(25.0%)	(24.4%)	(22.7%)	(23.0%)	(22.4%)	(39.2%)	(36.4%)	(32.1%)
COAD	160 (65.8%)	0	5 (2.1%)	4 (1.7%)	15 (6.6%)	17 (7.7%)	19 (8.9%)	11 (5.3%)	12 (6.0%)	8 (4.1%)	21 (10.8%)	16 (8.6%)	10 (5.4%)
Abdominal pain	52 (21.4%)	6 (2.5%)	14 (5.8%)	7 (3.0%)	5 (2.2%)	4 (1.8%)	1 (0.5%)	2 (1.0%)	1 (0.5%)	1 (0.5%)	0	3 (1.6%)	2 (1.1%)
Diarrhoea	47 (19.3%)	2 (0.8%)	16 (6.6%)	5 (2.1%)	4 (1.8%)	5 (2.3%)	2 (0.9%)	1 (0.5%)	2 (1.0%)	1 (0.5%)	3 (1.5%)	0	0
Injury	28 (11.5%)	0	0	0	0	0	1 (0.5%)	3 (1.4%)	1 (0.5%)	3 (1.5%)	2 (1.0%)	5 (2.7%)	2 (1.1%)
Back pain	24 (9.9%)	0	1 (0.4%)	1 (0.4%)	1 (0.4%)	2 (0.9%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	2 (1.0%)	2 (1.1%)	2 (1.1%)
Headache	33 (13.6%)	4 (1.6%)	14 (5.8%)	3 (1.3%)	2 (0.9%)	2 (0.9%)	2 (0.9%)	0	0	1 (0.5%)	2 (1.0%)	2 (1.1%)	0
Rhinitis	31 (12.8%)	0	1 (0.4%)	2 (0.8%)	2 (0.9%)	2 (0.9%)	1 (0.5%)	1 (0.5%)	2 (1.0%)	3 (1.5%)	6 (3.1%)	3 (1.6%)	1 (0.5%)
URTI	20 (8.2%)	0	0	1 (0.4%)	1 (0.4%)	1 (0.5%)	2 (0.9%)	2 (1.0%)	1 (0.5%)	0	1 (0.5%)	2 (1.1%)	3 (1.6%)
Prior SB-207499		n=480	n=479	n=468	n=465	n=459	n=451	n=444	n=438	n=435	n=431	n=413	n=402
	446	23	89	71	91	112	111	93	94	83	161	138	123
Total²	(92.9%)	(4.8%)	(18.6%)	(15.2%)	(19.6%)	(24.4%)	(24.6%)	(20.9%)	(21.5%)	(19.1%)	(37.4%)	(33.4%)	(30.6%)
COAD	334 (69.6%)	1 (0.2%)	25 (5.2%)	23 (4.9%)	28 (6.0%)	35 (7.6%)	30 (6.7%)	23 (5.2%)	25 (5.7%)	21 (4.8%)	35 (8.1%)	16 (3.9%)	22 (5.5%)
Abdominal pain	66 (13.8%)	1 (0.2%)	10 (2.1%)	4 (0.9%)	6 (1.3%)	4 (0.9%)	7 (1.6%)	0	6 (1.4%)	2 (0.5%)	6 (1.4%)	3 (0.7%)	1 (0.2%)
Diarrhoea	55 (11.5%)	2 (0.4%)	11 (2.3%)	6 (1.3%)	2 (0.4%)	4 (0.9%)	5 (1.1%)	4 (0.9%)	2 (0.5%)	1 (0.2%)	3 (0.7%)	4 (1.0%)	1 (0.2%)
Injury	67 (14.0%)	0	1 (0.2%)	1 (0.2%)	2 (0.4%)	2 (0.4%)	6 (1.3%)	2 (0.5%)	2 (0.5%)	7 (1.6%)	7 (1.6%)	5 (1.2%)	10 (2.5%)
Back pain	58 (12.1%)	1 (0.2%)	3 (0.6%)	2 (0.4%)	6 (1.3%)	4 (0.9%)	6 (1.3%)	2 (0.5%)	1 (0.2%)	2 (0.5%)	5 (1.2%)	4 (1.0%)	8 (2.0%)
Headache	47 (9.8%)	1 (0.2%)	10 (2.1%)	3 (0.6%)	3 (0.6%)	5 (1.1%)	3 (0.7%)	1 (0.2%)	1 (0.2%)	1 (0.2%)	4 (0.9%)	4 (1.0%)	2 (0.5%)
Rhinitis	46 (9.6%)	1 (0.2%)	4 (0.8%)	1 (0.2%)	1 (0.2%)	3 (0.7%)	3 (0.7%)	1 (0.2%)	1 (0.2%)	3 (0.7%)	6 (1.4%)	4 (1.0%)	2 (0.5%)
URTI	53 (11.0%)	0	0	1 (0.2%)	0	3 (0.7%)	5 (1.1%)	6 (1.4%)	5 (1.1%)	0	6 (1.4%)	3 (0.7%)	4 (1.0%)

Data Source: Section 15, [Table 15.5](#)

NOTE: Day 1 = Day 1 of study 040

1. Number of subjects reporting at least one AE during the study.

2. (%) = number of subjects reporting at least one AE during the time interval. Percentages are based on the number of subjects at each time interval.

During the early part of the study (up to approximately Day 56) the incidence of experiences was higher in the subjects who had previously received placebo than in subjects who had previously been treated with SB-207499. The incidence of gastrointestinal experiences was higher in the prior placebo group in the first days of the study as shown in [Table 21](#).

Table 21 Incidence of Gastrointestinal Adverse Experiences over Days 1 to 84

	1 day	2-7 days	8-14 days	15-28 days	29-56 days	57-84 days
Placebo¹	5.3%	19.8%	5.5%	6.2%	5.0%	2.8%
SB-207499¹	2.1%	8.1%	3.4%	3.0%	2.4%	4.2%
Total	3.2%	12.1%	4.1%	4.0%	3.2%	3.8%

Source data: Section 15, [Table 15.5](#)

1. Treatment received during study 042 or study 091

The cumulative incidences of nausea, abdominal pain, and all gastrointestinal adverse experiences of concern by time of initial onset and prior treatment are presented graphically in Section 19, [Figure 19.15](#), [Figure 19.16](#), and [Figure 19.17](#), respectively.

7.2.5. Adverse Experiences that Led to a Dose Interruption

The incidence of adverse experiences which led to an interruption in dosing are summarised in Section 15, [Table 15.6](#). (Adverse experiences which led to permanent discontinuation of study medication are discussed in Section [7.4](#)). A total of 102 subjects (14.1%) had dosing interrupted due to adverse experiences. Adverse experiences of the gastrointestinal system (seen in 50 subjects, 6.9%) were the most frequently occurring experiences that led to a dose interruption. Chronic obstructive airways disease, reported by 28 subjects (3.9%) was the most common individual experience which led to a dose interruption.

7.2.6. Adverse Experiences Requiring Corrective Treatment

Adverse experiences which required corrective treatment are summarised in Section 15, [Table 15.7](#). The number (%) of subjects with the most frequently reported adverse experiences ($\geq 5\%$ subjects in total) that required corrective therapy is shown in [Table 22](#).

Table 22 **Number (%) of Subjects with the Most Common (≥5% Subjects) On-Therapy Adverse Experiences That Required Corrective Therapy**

Adverse Experience (Preferred Term)	Prior SB-207499		Total (N = 723)
	Prior Placebo (N = 243)	15 mg bd N = 480)	
Total	199 (81.9%)	410 (85.4%)	609 (84.2%)
Chronic obstructive airways disease	150 (61.7%)	318 (66.3%)	468 (64.7%)
Injury	20 (8.2%)	51 (10.6%)	71 (9.8%)
Back pain	20 (8.2%)	44 (9.2%)	64 (8.9%)
Abdominal pain	24 (9.9%)	32 (6.7%)	56 (7.7%)
Rhinitis	19 (7.8%)	33 (6.9%)	52 (7.2%)
Upper respiratory tract infection	15 (6.2%)	32 (6.7%)	47 (6.5%)
Dyspepsia	18 (7.4%)	27 (5.6%)	45 (6.2%)
Pharyngitis	11 (4.5%)	29 (6.0%)	40 (5.5%)
Viral infection	13 (5.3%)	27 (5.6%)	40 (5.5%)
Arthralgia	17 (7.0%)	22 (4.6%)	39 (5.4%)
Headache	18 (7.4%)	20 (4.2%)	38 (5.3%)

Data Source: Section 15, [Table 15.7](#)

Chronic obstructive airways disease was by far the most frequently reported experience requiring corrective therapy, occurring in 468 subjects (64.7%). Overall, adverse experiences requiring corrective treatment occurred in similar percentages of both prior treatment groups.

7.2.7. Post Treatment Adverse Experiences

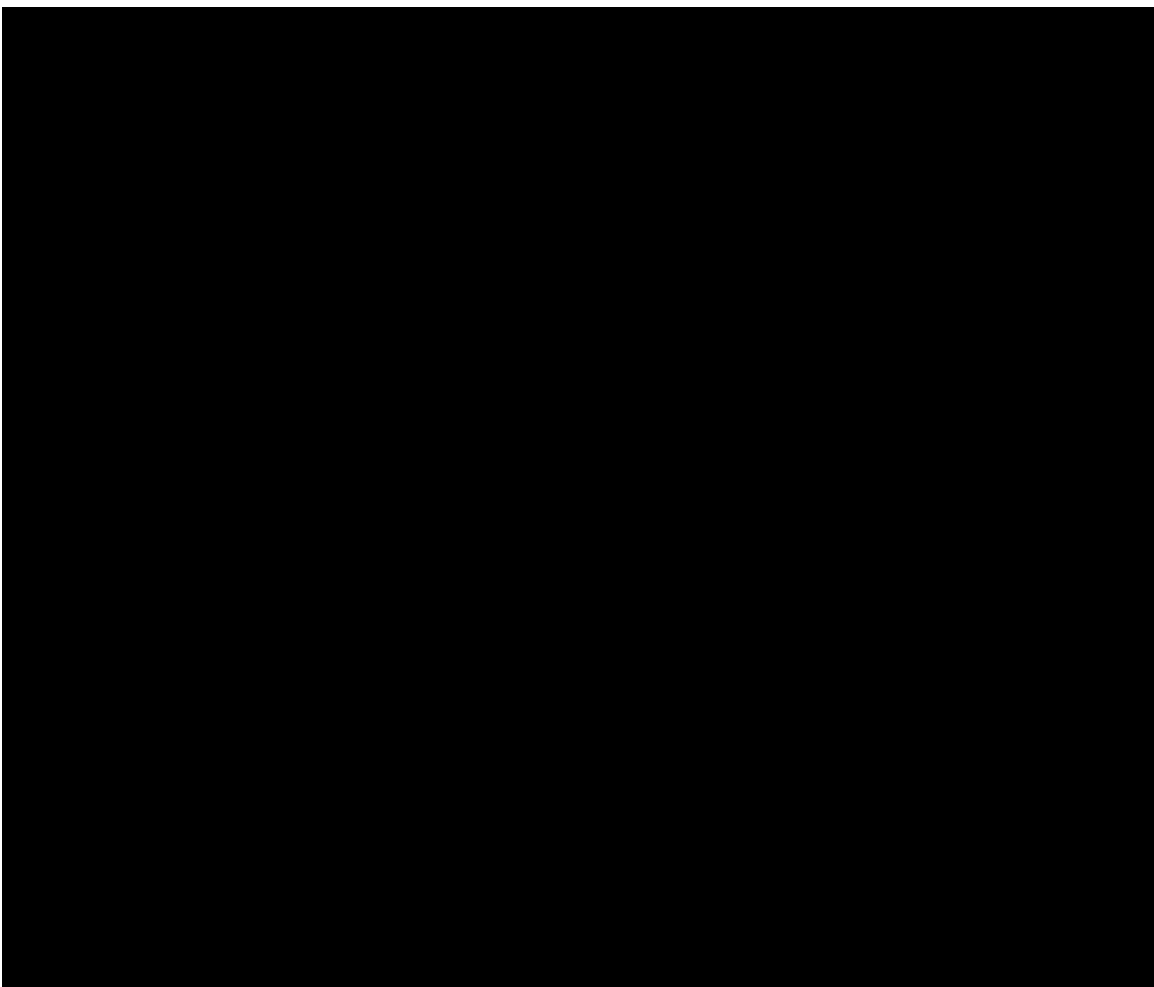
Adverse experiences which occurred in the post-therapy period are shown in Section 15, [Table 15.10](#). A total of 80 subjects (11.1%) reported adverse experiences post treatment. Chronic obstructive airways disease was the most commonly occurring experience, reported by 24 subjects (3.3%).

7.3. Serious Adverse Experiences

Fatal and non-fatal on-therapy and post-therapy serious adverse experiences (see Definitions) are presented in Section 15, [Table 15.8A](#) and [Table 15.8B](#), respectively. Case narratives for all subjects who died or who experienced a serious adverse experience are provided in [Section 20](#).

7.3.1. Fatal Experiences

A total of 24 subjects died during the study (see case narratives in [Section 20](#)), of whom 15 (3.1%) were in the prior SB-207499 treatment group and 9 (3.7%) were in the prior placebo treatment group. Fifteen deaths were due to adverse experiences that commenced whilst the subject was on study medication and 9 were due to adverse experiences which started in the post-treatment period as summarised in [Table 23](#). None of the deaths was considered by the Investigator to be related to study medication.

Table 23 Subject Deaths

Note: Total number of subjects in prior placebo group was 243 and total number in prior SB-207499 group was 480.

1. Refers to treatment during study 040 only.
2. Adverse experience commenced in the post-treatment period.
3. Subject died approximately 3 months after stopping study medication and data listings show outcome of event as unresolved.

7.3.2. Serious Adverse Experiences

Serious adverse experiences (both fatal and non-fatal) which occurred whilst the subject was on study drug therapy are presented in Section 15, [Table 15.8A](#).

A total of 203 subjects (28.1%) experienced serious adverse experiences during treatment. Experiences related to the respiratory system were the experiences most frequently recorded (93 subjects, 12.9%). The incidence of serious adverse experiences was similar in the two prior treatment groups. The most frequently occurring serious adverse experiences (occurring in $\geq 1\%$ of subjects) whilst on therapy in the study are summarised in [Table 24](#).

Table 24 Number (%) of Subjects with the Most Frequently Reported ($\geq 1.0\%$ Subjects) On-Therapy Serious Adverse Experiences

Adverse Experience (Preferred Term)	Prior Placebo (N = 243)	Prior SB-207499	
		15 mg bd (N = 480)	Total (N = 723)
Total	69 (28.4%)	134 (27.9%)	203 (28.1%)
Chronic obstructive airways disease	23 (9.5%)	44 (9.2%)	67 (9.3%)
Pneumonia ¹	6 (2.5%)	13 (2.7%)	19 (2.6%)
Injury	2 (0.8%)	15 (3.1%)	17 (2.4%)
Pulmonary carcinoma	2 (0.8%)	9 (1.9%)	11 (1.5%)
Angina pectoris	3 (1.2%)	5 (1.0%)	8 (1.1%)
Chest pain	3 (1.2%)	5 (1.0%)	8 (1.1%)
Neoplasm NOS	3 (1.2%)	5 (1.0%)	8 (1.1%)

Data Source: Section 15, [Table 15.8A](#)

1. Includes lobar pneumonia.

NOS = not otherwise specified

The most frequently occurring on-therapy serious adverse experience was chronic obstructive airways disease (i.e., COPD exacerbation) which occurred in 67 subjects (9.3%).

Six subjects (four in the prior placebo treatment group and two in the prior SB-207499 treatment group) had serious adverse experiences that were considered by the Investigator to be possibly (suspected) related to study medication.

[REDACTED]

Further details of all these experiences may be found in the case narratives located in [Section 20](#).

Of the 203 subjects with serious adverse experiences during the on-therapy period, 61 subjects were withdrawn from the study (see [Section 7.4](#)).

A total of 31 subjects (4.3%), (10 subjects (4.1%) in the prior placebo group, and 21 subjects (4.4%) in the prior SB-207499 group) experienced post-therapy, SAEs (Section 15, [Table 15.8B](#)). The only serious adverse experiences that occurred in more than two subjects during the post-therapy period were chronic obstructive pulmonary disease (5 subjects, 0.7%), cardiac arrest and pneumonia (each 4 subjects, 0.6%) and pulmonary carcinoma (3 subjects, 0.4%). None of the post-therapy experiences was considered by the Investigator to be related to study medication.

7.4. Adverse Experiences Leading to Premature Discontinuation of Investigational Product and/or Study

Adverse experiences which occurred while the subject was on therapy and which led to withdrawal of more than one subject are presented by preferred term in decreasing frequency of occurrence in Section 15, [Table 15.9A](#) and by body system and preferred term in Section 15, [Table 15.9B](#). Case narratives may be found in [Section 20](#). Within these data from [Table 15.9a](#) it was possible to assign more than one AE to a patient withdrawal, consequently the numbers of AE's is significantly higher than the total number of patients withdrawn. Figures for individual AE's therefore represent the number of patients for which the AE's contributed to withdrawal rather than being the number of patients for which the AE was the primary cause of withdrawal. A total of 123 subjects (17.0%) were withdrawn from the study because of adverse experiences which commenced whilst on therapy in this study. (A further 12 subjects withdrew for adverse events which commenced prior to the start date of study 040 and this accounts for the disparity in the numbers of subjects withdrawn between [Table 15.9A](#) and [Table 13.3](#)). The proportion of subjects withdrawn because of adverse experiences was higher for the group who had previously received placebo (22.2%) compared with the prior SB-207499 treatment group (14.4%). Adverse experiences of the gastrointestinal system were the most frequent reason for withdrawal (45 subjects, 6.2%) and these occurred more frequently in the prior placebo group compared with the prior SB-207499 group (9.5% versus 4.6%). Forty-seven subjects were withdrawn due to adverse experiences that were considered by the Investigator to be drug-related (suspected or probable).

The number (%) of adverse experiences leading to withdrawal of more than two subjects is summarised in [Table 25](#).

Table 25 Number (%) of Subjects with Adverse Experiences Which Led to Withdrawal of More Than Two Subjects

Adverse Experience (Preferred Term)	Prior SB-207499		Total (N = 723)
	Prior Placebo (N = 243)	15 mg bd (N = 480)	
Total ¹	54 (22.2%)	69 (14.4%)	123 (17.0%)
Abdominal pain	13 (5.3%)	11 (2.3%)	24 (3.3%)
Chronic obstructive airways disease	5 (2.1%)	8 (1.7%)	13 (1.8%)
Nausea	8 (3.3%)	3 (0.6%)	11 (1.5%)
Pulmonary carcinoma	2 (0.8%)	9 (1.9%)	11 (1.5%)
Diarrhoea	6 (2.5%)	4 (0.8%)	10 (1.4%)
Vomiting	6 (2.5%)	2 (0.4%)	8 (1.1%)
Pneumonia	2 (0.8%)	3 (0.6%)	5 (0.7%)
Aneurysm	2 (0.8%)	1 (0.2%)	3 (0.4%)
Carcinoma	1 (0.4%)	2 (0.4%)	3 (0.4%)
Headache	2 (0.8%)	1 (0.2%)	3 (0.4%)

Data Source: Section 15, [Table 15.9A](#)

1. Total represents total number of subjects withdrawn due to an adverse experience.

Note. For figures other than the total. Figures for individual AE's represent the number of patients for which the AE's contributed to withdrawal rather than the number of patients for which the AE was the primary cause of withdrawal.

Abdominal pain was the most commonly occurring experience which led to withdrawal and this occurred more frequently in subjects in the prior placebo treatment group.

On-therapy adverse experiences that led to dose interruption are provided by prior treatment in Section 15, [Table 15.6](#) (see Section 7.2.5).

7.5. Gastrointestinal Adverse Experiences of Concern

The number and percentage of subjects with on-therapy GIAEs of concern is provided by treatment group and preferred term in Section 15, [Table 15.11A](#). The incidence of GIAEs of concern that led to withdrawal is summarised in Section 15, [Table 15.11B](#). The cumulative incidence of GIAEs of concern by time of initial onset and prior treatment in is presented graphically in Section 19, [Figure 19.17](#). Case narratives for all subjects with GIAEs of clinical concern are provided in [Section 20](#).

A total of 97 subjects (13.4%) reported 151 GIAEs of concern. These were reported by a higher proportion of subjects in the prior placebo group than in the prior SB-207499 group (17.3% versus 11.5%). GIAEs of concern that were reported by more than one subject are summarised in [Table 26](#).

Table 26 Number (%) of Subjects with On-Therapy Gastrointestinal Adverse Experiences of Concern Reported by More Than One Subject

Adverse Experience (Preferred Term)	Prior SB-207499		Total (N = 723)
	Prior Placebo (N = 243)	15 mg bd (N = 480)	
Total ¹	42 (17.3%)	55 (11.5%)	97 (13.4%)
Abdominal pain	22 (9.1%)	22 (4.6%)	44 (6.1%)
Diarrhoea	17 (7.0%)	14 (2.9%)	31 (4.3%)
Vomiting	9 (3.7%)	5 (1.0%)	14 (1.9%)
Nausea	8 (3.3%)	5 (1.0%)	13 (1.8%)
Dyspepsia	7 (2.9%)	3 (0.6%)	10 (1.4%)
Gastritis	3 (1.2%)	2 (0.4%)	5 (0.7%)
Melaena	3 (1.2%)	2 (0.4%)	5 (0.7%)
Constipation	0	3 (0.6%)	3 (0.4%)
GI haemorrhage	2 (0.8%)	1 (0.2%)	3 (0.4%)
Gastroenteritis	0	2 (0.4%)	2 (0.3%)
Gastrointestinal disorder NOS	0	2 (0.4%)	2 (0.3%)
Haemorrhoids	0	2 (0.4%)	2 (0.3%)
Intestinal obstruction	1 (0.4%)	1 (0.2%)	2 (0.3%)
Neoplasm NOS	0	2 (0.4%)	2 (0.3%)

Data Source: Section 15, [Table 15.11A](#)

1. Total represents total number of subjects reporting at least one GI adverse experience of concern.

NOS=not otherwise specified

Overall, the two most commonly reported GIAEs of concern were abdominal pain, reported by 44 subjects (6.1%) and diarrhoea, reported by 31 subjects (4.3%). These experiences occurred in a higher percentage of subjects who previously received placebo.

The majority (87%) of the 151 GIAEs were mild or moderate in severity and were considered to be related (suspected or probable) to study medication by the Investigator.

Thirty-three subjects (4.6%) were withdrawn from the study due to GIAEs of concern (Section 15, [Table 15.11B](#)). There was a higher rate of withdrawal (18 subjects, 7.4%) from the prior placebo treatment group than from the prior SB-207499 treatment group (15 subjects, 3.1%). Abdominal pain was the experience, which most frequently led to withdrawal, being reported by 20 subjects (2.8%) in total. Of these, 12 subjects were in the prior placebo group.

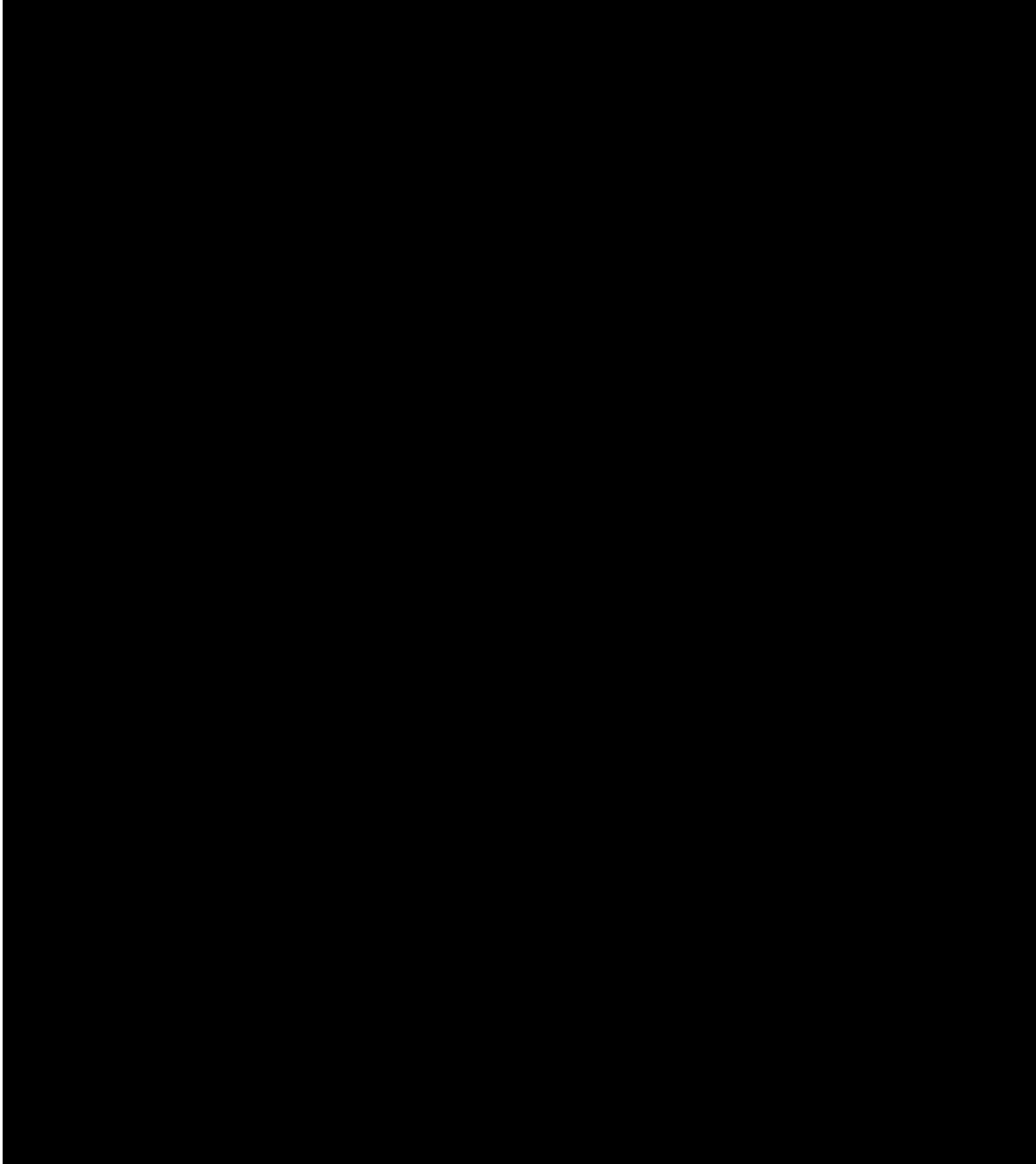
Of the 97 subjects who had on-therapy GIAEs of concern, 70 had faecal occult blood tests performed (Section 15, [Table 15.12A](#)). [REDACTED]

[REDACTED] These five subjects are included in [Table 27](#).

Stool assessment at the time of the GIAE of concern showed that 11 subjects (6 in the prior SB-207499 group and 5 in the prior placebo group) had blood in their stool or their stools had a dark, tarry appearance. Faecal occult blood tests at the time of the GIAE of concern were carried out for 6 of these 11 subjects and two had positive results. [REDACTED]

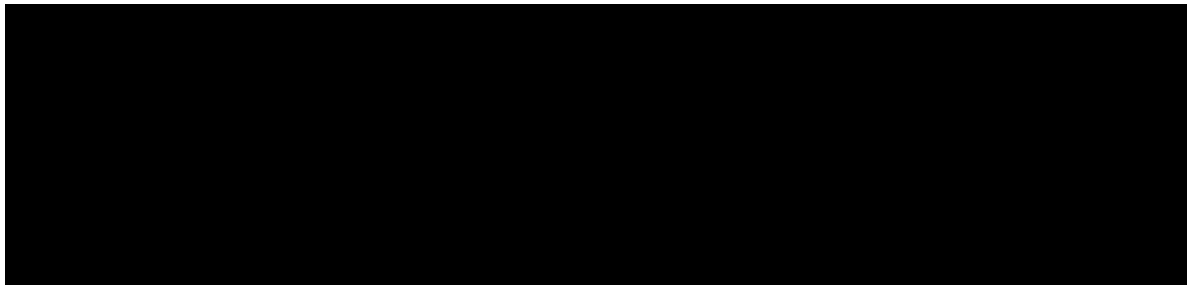
[REDACTED] Details of the 14 subjects who had either blood in their stool or a positive FOB test result at the time of their GIAE of concern are provided in [Table 27](#).

Table 27 **Details of Subjects with Blood in Stool or Positive Faecal Occult
Blood Test When Reporting a Gastrointestinal Adverse Experience
of Concern**



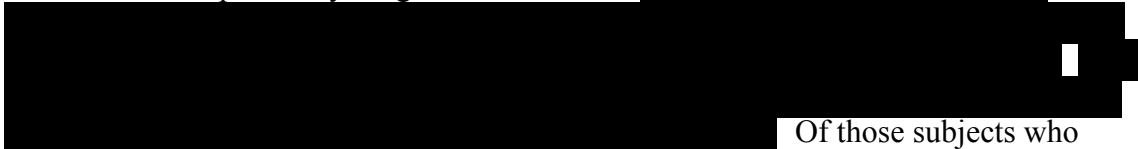
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Table 27 **Details of Subjects with Blood in Stool or Positive Faecal Occult Blood Test When Reporting a Gastrointestinal Adverse Experience of Concern (Continued)**



1. Drug-related refers to investigator opinion of relationship of AE to study drug. No=not related/unlikely to be related. Yes=Suspected/Probably related.
2. Faecal occult blood test result taken at time of GIAE of concern.
3. sBP=systolic blood pressure, dBP=diastolic blood pressure, HR= heart rate at time of GIAE of concern. High value for sBP is a decrease of 10-19. Values of concern are decrease of ≥ 20 for sBP, decrease of ≥ 10 for dBP and increase of ≥ 10 for HR.
4. Hb=haemoglobin taken at time of GIAE of concern. Value of low concern is $< 0.8 \times \text{LLN}$ (lower limit of normal), low value is $0.8-1 \times \text{LLN}$, high value is $1-1.2 \times \text{ULN}$ (upper limit of normal)
5. Positive on routine faecal occult blood test. Subsequent examination by colonoscopy revealed sigmoid diverticulosis and rectal polyps.

The adverse experiences reported by these fourteen subjects were suspected by the investigator to be study drug-related in four subjects; three of these subjects reported black, tarry stools and one subject had normal stool with red blood on the outside (the reported adverse experience was dyspepsia). Two of these patients with a suspected event relationship to study drug were withdrawn.



Of those subjects who continued in the study, none suffered a reoccurrence of a GIAE event and none experienced a further positive faecal occult blood test result at any of the routine annual tests. The mean time on treatment post GIAE without recurrence of a GIAE of concern or a further positive FOB result was 612.2 days.

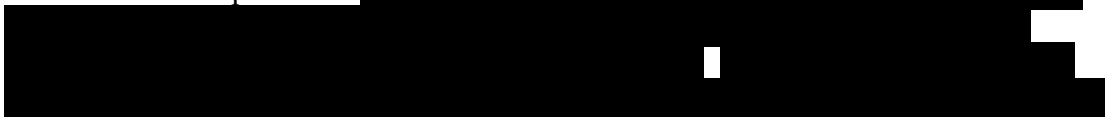
Of the 14 subjects in [Table 27](#), only three were not followed up by endoscopy.



The three GI haemorrhage GIAEs were all investigated via upper digestive endoscopy.



This subject continued on therapy without recurrence of the problem.



[REDACTED] All three GI haemorrhage events were of suspected relationship to study drug. [REDACTED]

Seven colonoscopies were undertaken. [REDACTED]

[REDACTED] Of all subjects who had on-therapy GIAEs of concern, 85 subjects had orthostatic vital signs measured at the time of the GIAE (Section 15, [Table 15.13A](#)). Of these, 6 subjects (three in each previous treatment group) had changes of clinical concern in systolic blood pressure (decrease of ≥ 20 mmHg), 17 subjects (6 who previously received placebo and 11 who previously received SB-207499) had changes of clinical concern in diastolic blood pressure (decrease of ≥ 10 mmHg) and 12 subjects (one who previously received placebo and 11 who previously received SB-207499) had changes of clinical concern in heart rate (increase of ≥ 10 bpm). The majority of these subjects had values at baseline that were not of clinical concern. Further information may be found in the case narratives in [Section 20](#).

During routine faecal occult blood testing 35 subjects were found to have trace blood 5.1% in the placebo group and 6% in the former cilomilast group producing (5.7% in total (Section 15, [Table 15.12B](#)). None of these positive events were associated with GIAE's of concern.

7.6. Pregnancies

No subject became pregnant during the course of the study.

7.7. Clinical Laboratory Evaluations

7.7.1. Faecal Occult Blood Tests

The incidence of subjects with positive findings on routine faecal occult blood testing is summarised in Section 15, [Table 15.12B](#). At baseline there were 613 negative tests, one positive test and three subjects with missing results. [REDACTED]

[REDACTED] A total of 35 subjects of the 617 tested (5.7%) had a positive test on therapy. No significant difference was seen between former placebo and former cilomilast groups 5.1% and 6% respectively). In general, positive tests were not associated with the reporting of GIAEs of concern (see Section [7.5](#)).

7.7.2. Clinical Laboratory Values over Time

Clinical chemistry and haematology parameters were measured at regular intervals throughout the study. The mean values and mean change from baseline of studies 042 and 091 are shown in Section 15, [Table 15.14](#).

Results at endpoint for selected haematological parameters are shown in [Table 28](#) and for selected clinical chemistry parameters in [Table 29](#).

Table 28 Mean Change from Baseline of Studies 042 and 091 in Selected Haematology Parameters in Study 040

Laboratory Variable	Prior Treatment Group	n	Assessment		Change from Baseline ^a	
			Mean	sd	Mean	sd
Haemoglobin (g/L)	Baseline ¹					
	Placebo	243	148.76	13.82		
	SB-207499	478	149.84	12.96		
	Endpoint ²					
	Placebo	240	146.43	15.81	-2.31	12.73
	SB-207499	472	146.72	14.07	-3.14	10.11
Haematocrit (%)	Baseline					
	Placebo	243	44.41	4.23		
	SB-207499	478	44.65	3.79		
	Endpoint					
	Placebo	240	44.05	4.67	-0.35	3.81
	SB-207499	472	44.23	4.35	-0.42	3.22
WBC (10⁹/L)	Baseline					
	Placebo	243	7.73	2.20		
	SB-207499	478	7.54	1.95		
	Endpoint					
	Placebo	240	7.50	2.35	-0.25	2.25
	SB-207499	472	7.58	2.12	0.03	1.93
Neutrophil (10⁹/L)	Baseline					
	Placebo	243	4.86	1.72		
	SB-207499	478	4.68	1.65		
	Endpoint					
	Placebo	240	4.77	1.90	-0.10	2.00
	SB-207499	472	4.86	1.79	0.17	1.81
Eosinophil (10⁹/L)	Baseline					
	Placebo	243	0.25	0.22		
	SB-207499	478	0.22	0.15		
	Endpoint					
	Placebo	240	0.23	0.26	-0.02	0.21
	SB-207499	472	0.21	0.16	-0.01	0.16
Platelets (10⁹/L)	Baseline					
	Placebo	243	232.64	62.78		
	SB-207499	478	241.46	70.56		
	Endpoint					
	Placebo	240	247.81	81.17	15.53	62.01
	SB-207499	472	256.73	79.50	14.99	58.37

Data Source: Section 15, [Table 15.14](#)

1. Baseline refers to the start of study 042 or study 091.
2. Endpoint refers to last value reported on therapy.

Table 29 Mean Change from Baseline of Studies 042 and 091 in Selected Clinical Chemistry Parameters in Study 040

Laboratory Variable	Prior Treatment Group	n	Assessment		Change from baseline ^a	
			Mean	sd	Mean	sd
AST (International Unit (IU)/L)						
Baseline ¹	Placebo	242	20.80	8.34		
	SB-207499	476	20.58	12.35		
Endpoint ²	Placebo	239	21.45	13.19	0.60	11.82
	SB-207499	472	21.00	13.81	0.33	16.07
ALT (IU/L)						
Baseline	Placebo	242	20.03	13.07		
	SB-207499	476	19.83	11.63		
Endpoint	Placebo	239	20.02	14.06	-0.08	13.20
	SB-207499	472	19.57	13.75	-0.35	14.14
GGT (IU/L)						
Baseline	Placebo	243	39.37	34.66		
	SB-207499	476	40.63	35.54		
Endpoint	Placebo	239	45.27	76.23	5.85	72.55
	SB-207499	472	47.40	74.43	6.19	62.81
Total Bilirubin (μmol/L)						
Baseline	Placebo	243	10.93	3.94		
	SB-207499	476	11.09	4.82		
Endpoint	Placebo	239	11.02	5.39	0.07	4.68
	SB-207499	472	11.18	5.36	0.07	4.56
Alkaline Phosphatase (IU/L)						
Baseline	Placebo	242	74.55	21.99		
	SB-207499	476	75.58	21.88		
Endpoint	Placebo	239	73.66	21.39	-0.47	15.65
	SB-207499	472	77.70	53.85	2.28	50.83
Creatinine (μmol/L)						
Baseline	Placebo	243	76.08	19.52		
	SB-207499	476	75.61	19.79		
Endpoint	Placebo	239	77.67	19.92	1.80	13.30
	SB-207499	472	75.46	22.38	-0.26	13.98
Blood Urea Nitrogen (BUN) (mmol/L)						
Baseline	Placebo	243	5.64	1.81		
	SB-207499	476	5.64	1.72		
Endpoint	Placebo	239	5.79	1.89	0.17	1.62
	SB-207499	472	5.71	1.89	0.06	1.52
Sodium (mmol/L)						
Baseline	Placebo	243	140.50	2.79		
	SB-207499	476	140.63	2.82		
Endpoint	Placebo	240	140.53	3.06	0.02	3.24
	SB-207499	472	140.76	2.80	0.17	3.54
Potassium (mmol/L)						
Baseline	Placebo	242	4.53	0.38		
	SB-207499	476	4.52	0.39		
Endpoint	Placebo	240	4.48	0.40	-0.05	0.46
	SB-207499	472	4.43	0.41	-0.09	0.47

Continued

Table 29 Mean Change from Baseline of Studies 042 and 091 in Selected Clinical Chemistry Parameters in Study 040 (Continued)

Laboratory Variable	Prior Treatment Group	n	Assessment		Change from baseline ^a	
			Mean	sd	Mean	sd
Glucose Random (mmol/L)						
Baseline	Placebo	242	6.11	1.88		
	SB-207499	476	6.09	2.24		
Endpoint	Placebo	239	6.30	2.05	0.19	1.88
	SB-207499	472	6.38	2.20	0.29	2.08
Uric Acid (μmol/L)						
Baseline	Placebo	243	324.79	91.46		
	SB-207499	476	324.71	82.56		
Endpoint	Placebo	239	329.64	93.03	5.15	77.75
	SB-207499	472	330.46	81.79	5.62	66.65

Data Source: Section 15, [Table 15.14](#)

1. Baseline refers to the start of study 042 or study 091.
2. Endpoint refers to last value reported on therapy.

Overall, mean changes from baseline were small and no trends for a treatment related effect on any parameter were seen.

7.7.3. Abnormalities of Potential Clinical Concern

Values of potential clinical concern were pre-defined by GlaxoSmithKline and are shown for selected variables in Section 5.8.5.3. The numbers (%) of subjects with on-therapy laboratory values of potential clinical concern for haematology and clinical chemistry variables are shown in Section 15, [Table 15.15](#). The percentage of subjects who showed a transition at any time on therapy from a normal result at baseline are shown in [Table 30](#) and [Table 31](#).

**Table 30 Transitions from Normal Range at Baseline for Haematology Values
– Time Point: On-therapy**

Variable	N ¹	Low Concern n (%)	Low n (%)	Normal n (%)	High n (%)	High Concern n (%)
Haemoglobin						
All Subjects	633	5 (0.8%)	91 (14.4%)	454 (71.7%)	86 (13.6%)	1 (0.2%)
Haematocrit						
All Subjects	606	3 (0.5%)	98 (16.2%)	328 (54.1%)	187 (30.9%)	2 (0.3%)
WBC						
All Subjects	663	6 (0.9%)	25 (3.8%)	410 (61.8%)	219 (33.0%)	6 (0.9%)
Neutrophil						
All Subjects	676	20 (3.0%)	31 (4.6%)	405 (59.9%)	190 (28.1%)	38 (5.6%)
Eosinophil						
All Subjects	680	ND	ND	573 (84.3%)	99 (14.6%)	8 (1.2%)
Platelet Count						
All Subjects	678	16 (2.4%)	35 (5.2%)	537 (79.2%)	70 (10.3%)	25 (3.7%)

Data Source: Section 15, [Table 15.15](#)

ND = Not defined.

1. Number of subjects with values within the normal range at baseline of study 042 or 091.

Note 1: Subjects with on-therapy values who meet criteria for both high and low values of interest and concern are reported in both categories, if applicable.

Note 2: Percentages are based on the number of subjects with values within the normal range at baseline.

Note 3: Subjects are assigned to categories based on their highest and/or lowest on-therapy value.

Table 31 Transitions from Normal Range at Baseline for Clinical Chemistry Laboratory Values - Time Point: On-therapy

Variable	N ¹	Low Concern n (%)	Low n (%)	Normal n (%)	High n (%)	High Concern n (%)
AST						
All Subjects	693	ND	ND	632 (91.2%)	48 (6.9%)	13 (1.9%)
ALT						
All Subjects	683	ND	ND	605 (88.6%)	64 (9.4%)	14 (2.0%)
GGT						
All Subjects	615	ND	ND	498 (81.0%)	94 (15.3%)	23 (3.7%)
Total Bilirubin						
All Subjects	688	ND	ND	594 (86.3%)	77 (11.2%)	17 (2.5%)
Alkaline Phosphatase						
All Subjects	688	ND	ND	644 (93.6%)	42 (6.1%)	2 (0.3%)
Creatinine						
All Subjects	679	1 (0.1%)	88 (13.0%)	537 (79.1%)	51 (7.5%)	3 (0.4%)
BUN						
All Subjects	693	ND	ND	609 (87.9%)	83 (12.0%)	1 (0.1%)
Sodium						
All Subjects	686	16 (2.3%)	84 (12.2%)	427 (62.2%)	142 (20.7%)	29 (4.2%)
Potassium						
All Subjects	683	3 (0.4%)	19 (2.8%)	518 (75.8%)	43 (6.3%)	101 (14.8%)
Glucose Random						
All Subjects	566	7 (1.2%)	109 (19.3%)	180 (31.8%)	140 (24.7%)	195 (34.5%)
Uric Acid						
All Subjects	692	ND	ND	622 (89.9%)	67 (9.7%)	3 (0.4%)

Data Source: Section 15, [Table 15.15](#)

ND = Not defined

1. Number of subjects with values within the normal range at baseline of study 042 or study 091.

Note 1: Subjects with on-therapy values who meet criteria for both high and low values of interest and concern are reported in both categories, if applicable.

Note 2: Percentages are based on the number of subjects with values within the normal range at baseline.

Note 3: Subjects are assigned to categories based on their highest and/or lowest on-therapy value.

Due to the length of the study and the large number of laboratory assessments performed for each subject, transitions to high or low values for laboratory values at any one point during the study were not uncommon. However, the numbers of subjects with transitions in haematology and chemistry parameters from normal at Baseline to potential clinical concern on-therapy were generally low. A large number of subjects showed shifts to high glucose values of concern but it should be noted that the glucose was measured from a random, not a fasted sample. The number of subjects with potassium levels of high concern was also high. However, when only shifts at endpoint were considered, only 8 subjects (1.2%) had values of high concern (Section 15, [Table 15.15](#)).

The following table shows a listing of subjects with laboratory values that were reported as adverse experiences during the study. A total of 170 subjects (23.5%) had laboratory values reported as adverse experiences (see [Table 32](#)); subjects may have reported more

than one laboratory value as an adverse experience. The majority of the adverse experiences were considered by the Investigator to be unrelated to study medication (i.e. not related or unlikely to be related).

Table 32 On-therapy Laboratory Values Reported as Adverse Experiences

Adverse Experience (Preferred Term)	Related to study medication	
	n (%)	n (%)
Hyperglycemia	37 (5.1%)	3 (0.4%)
Leukocytosis	23 (3.2%)	0
Albuminuria	18 (2.5%)	0
Gamma GT increased	17 (2.4%)	5 (0.7%)
Hepatic enzymes increased	16 (2.2%)	4 (0.6%)
Anaemia	13 (1.8%)	2 (0.3%)
Hypercholesterolaemia	13 (1.8%)	1 (0.1%)
Gout	12 (1.7%)	0
Hyperuricaemia	10 (1.4%)	1 (0.1%)
Diabetes mellitus	9 (1.2%)	0
Glycosuria	8 (1.1%)	0
SGPT increased	8 (1.1%)	3 (0.4%)
Hepatic function abnormal	7 (1.0%)	1 (0.1%)
Hyperthyroidism	7 (1.0%)	0
Hypoglycaemia	7 (1.0%)	0
Polycythaemia	6 (0.8%)	0
Bilirubinaemia	5 (0.7%)	3 (0.4%)
Blood urea nitrogen increased	5 (0.7%)	3 (0.4%)
Hyperlipaemia	5 (0.7%)	0
Hypernatraemia	5 (0.7%)	3 (0.4%)
SGOT increased	5 (0.7%)	1 (0.1%)
Hyperkalaemia	3 (0.4%)	2 (0.3%)
Hypokalaemia	3 (0.4%)	1 (0.1%)
Hyponatraemia	3 (0.4%)	0
Hypothyroidism	3 (0.4%)	0
Alkaline phosphatase increased	3 (0.4%)	0
Leukopenia	3 (0.4%)	0
NPN increased	3 (0.4%)	0
Diabetes mellitus aggravated	2 (0.3%)	0
Eosinophilia	2 (0.3%)	0
Granulocytopenia	2 (0.3%)	0
Hypochloraeaemia	2 (0.3%)	0
Thrombocytopenia	2 (0.3%)	0
Erythrocytes abnormal	1 (0.1%)	0
Glucose tolerance abnormal	1 (0.1%)	1 (0.1%)
Hypertriglyceridaemia	1 (0.1%)	0
Hypocholesterolaemia	1 (0.1%)	0
Hypochromic anaemia	1 (0.1%)	0
Ketosis	1 (0.1%)	0
Macrocytic anaemia	1 (0.1%)	0
Serum iron decreased	1 (0.1%)	0

Data Source: Section 15, [Table 15.2B](#) and [Table 15.3](#)

7.8. Vital Signs

Sitting systolic and diastolic blood pressures and heart rates were recorded at each study visit. Mean vital sign values and changes from baseline of studies 042 and 091 are presented in Section 15, [Table 15.16](#) at all study visits. Change in vital signs at study Endpoint are summarised in [Table 33](#).

Table 33 Mean Change from Baseline of Studies 042 and 091 in Sitting Vital Sign Values at Endpoint in Study 040

		Assessment			Change from Baseline	
Week of Treatment	Prior Treatment Group	n	Mean	sd	Mean	sd
Systolic BP, mmHg						
Baseline ¹	Placebo	243	135.2	17.1		
	SB-207499	480	134.3	18.0		
Endpoint ²	Placebo	240	134.2	16.0	-1.1	15.6
	SB-207499	473	132.0	16.2	-2.3	17.0
Diastolic BP, mmHg						
Baseline ¹	Placebo	243	79.1	9.7		
	SB-207499	480	79.1	9.6		
Endpoint ²	Placebo	240	78.2	9.7	-0.9	9.6
	SB-207499	473	76.9	10.3	-2.2	10.2
Heart Rate, bpm						
Baseline ¹	Placebo	243	76.8	9.6		
	SB-207499	480	76.3	10.7		
Endpoint ²	Placebo	240	76.7	11.8	-0.2	12.7
	SB-207499	473	76.5	12.3	0.3	12.2

Data Source: Section 15, [Table 15.16](#)

1. Baseline refers to the start of study 042 or study 091.
2. Endpoint refers to last value reported on therapy.

Only small changes from baseline were seen in vital signs throughout the study.

The number (%) of subjects with on-therapy vital sign values of potential clinical concern at any time during the study is presented in Section 15, [Table 15.17](#). The criteria used to define values of potential clinical concern are shown in Section [5.8.5.3](#).

The percentage of subjects with transitions in sitting systolic blood pressure, diastolic blood pressure, and heart rate from normal at baseline to sponsor-defined potential clinical concern on-therapy ranged from 0.5% to 2.2% and are summarised in [Table 34](#).

Table 34 Transitions from Normal Range at Baseline for Sitting Vital Signs – Time Point: On-therapy

Variable	N ¹	Low Concern n (%)	Low n (%)	Normal n (%)	High n (%)	High Concern n (%)
Sitting Systolic BP, mmHg						
All Subjects	404	0	10 (2.5%)	110 (27.2%)	282 (69.8%)	4 (1.0%)
Sitting Diastolic BP, mmHg						
All Subjects	594	6 (1.0%)	57 (9.6%)	275 (46.3%)	266 (44.8%)	3 (0.5%)
Heart Rate, bpm						
All Subjects	673	15 (2.2%)	118 (17.5%)	404 (60.0%)	140 (20.8%)	8 (1.2%)

Data Source: Section 15, [Table 15.17](#)

1. Number of subjects with values within the normal range at baseline of studies 042 or 091.

Note 1: Subjects with on-therapy values who meet criteria for both high and low values of interest and concern are reported in both categories, if applicable.

Note 2: Percentages are based on the number of subjects with values within the normal range at baseline.

Note 3: Subjects are assigned to categories based on their highest and/or lowest on-therapy value.

Due to the length of the study and the large number of vital signs assessments performed for each subject, transitions to high or low values at any one point during the study were not uncommon (see [Table 34](#)). However, at endpoint, the number of transitions to values of concern was low and the mean values were normal, indicating that any changes were transient.

Orthostatic vital signs were also measured at 24 and 48 weeks and then every 48 weeks thereafter including early withdrawal or visits associated with GIAEs of concern if relevant. Results associated with GIAEs of concern are shown in Section 15, [Table 15.13A](#) and discussed in Section 7.5. Changes in orthostatic vital signs throughout the study are shown in Section 15, [Table 15.13B](#).

The percentage of subjects with orthostatic changes in systolic blood pressure, diastolic blood pressure, and heart rate from normal to potential clinical concern (see Section 5.8.5.3) on-therapy are shown in [Table 35](#).

Table 35 Transitions from Normal Range at Baseline for Orthostatic Vital Signs – Time Point: On-therapy

Variable	N ¹	Normal n (%)	High n (%)	Concern n (%)
Orthostatic change in Systolic BP, mmHg				
All Subjects	608	440 (72.4%)	138 (22.7%)	30 (4.9%)
Orthostatic change in Diastolic BP, mmHg				
All Subjects	664	568 (85.5%)	-	96 (14.5%)
Orthostatic change in Heart Rate, bpm				
All Subjects	659	570 (86.5%)	-	89 (13.5%)

Data Source: Section 15, [Table 15.13B](#)

1. Number of subjects with values within the normal range at baseline of study 042 or study 091

Note 1: Subjects with on-therapy values who meet criteria for both high and low values of interest and concern are reported in both categories, if applicable.

Note 2: Percentages are based on the number of subjects with values within the normal range at baseline.

Note 3: Subjects are assigned to categories based on their highest and/or lowest on-therapy value.

The number of subjects who had vital signs reported as adverse experiences is summarised in [Table 36](#). The majority of these experiences were considered by the Investigator to be unrelated to study medication.

Table 36 Number (%) Subjects Reporting Vital Sign Changes as Adverse Experiences

Adverse Experience	n (%)	Related to study drug n (%)
Hypertension	45 (6.2%)	2 (0.3%)
Hypertension aggravated	9 (1.2%)	0
Hypotension	6 (0.8%)	2 (0.3%)
Postural hypotension	5 (0.7%)	1 (0.1%)
Pulmonary hypertension	1 (0.1%)	0

Source Data: Section 15, [Table 15.2B](#) and [Table 15.3](#)

7.9. Electrocardiographic Data

Standard 12-lead ECGs (at trough) were performed at all visits. Mean changes in ECG parameters from baseline at all study visits are presented in Section 15, [Table 15.18](#). Mean changes from baseline in selected ECG parameters are shown in [Table 37](#).

Table 37 Changes from Baseline of Study 042 or Study 091 in Mean Trough 12-Lead ECG Values at Endpoint

			Assessment		Change from Baseline	
Week of Treatment	Prior Treatment Group	n	Mean	sd	Mean	sd
Atrial Rate, bpm						
Baseline ¹	Placebo	243	74.0	12.2		
	SB-207499	478	74.1	12.8		
Endpoint ²	Placebo	239	75.8	13.9	1.7	12.8
	SB-207499	471	76.1	14.5	2.2	13.4
Ventricular Rate, bpm						
Baseline ¹	Placebo	243	74.0	12.3		
	SB-207499	480	74.1	12.8		
Endpoint ²	Placebo	239	75.8	13.9	1.7	12.8
	SB-207499	471	76.1	14.5	2.2	13.4
PR Interval, msec						
Baseline ¹	Placebo	238	156.1	23.5		
	SB-207499	471	158.8	25.8		
Endpoint ²	Placebo	234	159.1	27.0	2.8	15.7
	SB-207499	466	160.3	27.5	1.2	16.2
QRS Interval, msec						
Baseline ¹	Placebo	243	93.3	15.4		
	SB-207499	480	92.9	15.6		
Endpoint ²	Placebo	239	94.2	17.6	0.8	10.3
	SB-207499	471	93.2	17.2	0.4	10.1
QT (uncorrected), msec						
Baseline ¹	Placebo	243	384.1	29.0		
	SB-207499	480	385.4	32.7		
Endpoint ²	Placebo	239	380.9	36.0	-2.9	31.8
	SB-207499	471	381.9	36.4	-4.0	32.7
QT (corrected), msec						
Baseline ¹	Placebo	243	423.1	22.0		
	SB-207499	480	424.1	21.6		
Endpoint ²	Placebo	239	423.5	25.3	0.3	21.1
	SB-207499	471	425.0	24.5	1.0	22.8
Axis, deg						
Baseline ¹	Placebo	243	33.2	48.6		
	SB-207499	480	37.2	46.9		
Endpoint ²	Placebo	239	29.7	50.0	-3.8	29.7
	SB-207499	471	34.6	47.6	-3.0	30.6
RR Interval, msec						
Baseline ¹	Placebo	243	832.5	136.2		
	SB-207499	480	834.8	149.1		
Endpoint ²	Placebo	239	818.1	152.1	-12.7	135.3
	SB-207499	471	817.1	156.7	-19.6	142.5

Data Source: Section 15, [Table 15.18](#)

1. Baseline refers to the start of study 042 or study 091.
2. Endpoint refers to last value reported on therapy.

Mean changes from baseline in ECG parameters were small.

Sponsor-defined ECG values of potential clinical concern or changes of potential clinical concern are defined in Section 5.8.5.3. The number of subjects with changes from baseline in ECG parameters is summarised for each clinic visit in Section 15, [Table 15.19A](#). The number of subjects with changes from baseline in QTc intervals of different magnitude at each clinic visit is summarised in Section 15, [Table 15.19B](#). The

number of subjects with any changes during the study from a normal value at baseline is summarised in [Table 38](#).

Table 38 Transitions from Normal Range at Baseline for Trough ECG Parameters – Time Point: On-therapy

Variable	N ¹	On-therapy				
		Low Concern n (%)	Low n (%)	Normal n (%)	High n (%)	High Concern n (%)
Atrial rate						
All Subjects	646	19 (2.9%)	87 (13.5%)	389 (60.2%)	134 (20.7%)	26 (4.0%)
Ventricular rate						
All Subjects	648	19 (2.9%)	88 (13.6%)	292 (45.1%)	138 (21.3%)	20 (3.1%)
QRS						
All Subjects	665	NA	NA	601 (90.4%)	64 (9.6%)	0
PR						
All Subjects	654	NA	NA	575 (87.9%)	78 (11.9%)	1 (0.2%)
QT (uncorrected)						
All Subjects	708	NA	NA	696 (98.3%)	NA	12 (1.7%)
QTc (corrected, absolute)						
All Subjects	508	NA	NA	225 (44.3%)	171 (33.7%)	112 (22.0%)
QTc (corrected, change)						
All Subjects	508	NA	NA	330 (65.0%)	144 (28.3%)	34 (6.7%)

Data Source: Section 15, [Table 15.19A](#) and [Table 15.19B](#).

NA = Not applicable

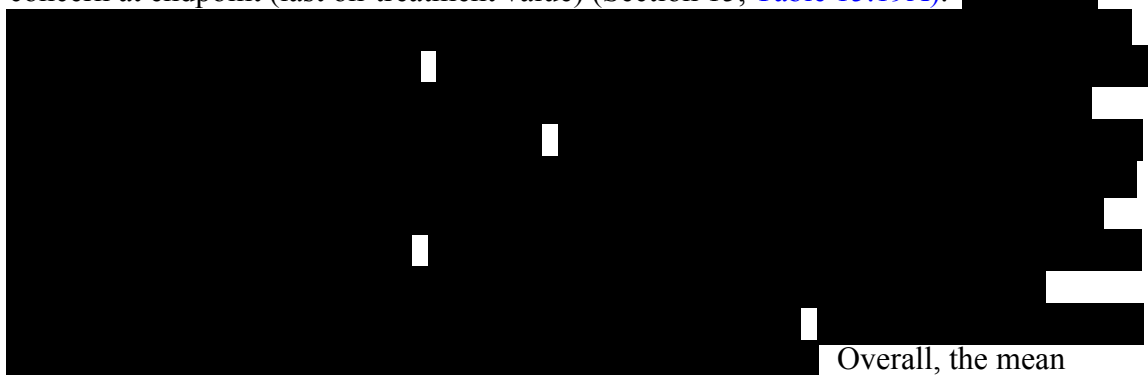
1. Number of subjects with values within the normal range at baseline of study 042 or study 091.

Note 1: Subjects with on-therapy values who meet criteria for both high and low values of interest and concern are reported in both categories, if applicable.

Note 2: Percentages are based on the number of subjects with values within the normal range at baseline.

Note 3: Subjects are assigned to categories based on their highest and/or lowest on-therapy value.

Due to the length of the study and the large number of ECGs performed for each subject, transitions to high or low values for ECG parameters at any one point during the study were not uncommon. The majority of subjects (approximately 75%) who had normal baseline values but high QTc values of concern on therapy only had isolated increases in QTc. Twenty-seven subjects (5.3%) who had a normal baseline value had a high value of concern at endpoint (last on-treatment value) (Section 15, [Table 15.19A](#)).



Overall, the mean change in QTc relative to baseline was no more than 1 msec (0.3 msec in the former placebo group and 1.0 msec in the former SB-207499 group). This has remained relatively stable relative to the feeder studies [[GSK Document Number SB-207499/RSD-100TKX/1](#); [GSK Document Number SB-207499/RSD-1017SH/1](#)] which demonstrated

changes of -0.1 msec and -0.8 msec in study 042 for placebo and SB-207499 respectively and no change and 0.7 msec change in study 091 for placebo and SB-207499 respectively. The numbers of subjects with transitions in atrial and ventricular rate, uncorrected QT, and PR from normal at Baseline to potential clinical concern on-therapy were low and there were no subjects with transitions in QRS.

The overall incidence of ECG abnormalities which occurred on therapy are shown in Section 15, [Table 15.20](#). The incidence of ECG abnormalities that occurred at any time during the study in $\geq 2\%$ of subjects are presented in [Table 39](#).

Table 39 New Onset ECG Abnormalities Occurring in $\geq 2\%$ of Subjects

ECG Abnormality	All Subjects (N = 723) n (%) ¹
QT interval increased	191 (30.7%)
Premature ventricular contractions NOS	172 (25.1%)
Sinus bradycardia	141 (23.0%)
Intraventricular block NOS	135 (20.1%)
Atrial hypertrophy NOS	140 (20.5%)
Premature atrial contractions NOS	142 (20.3%)
Poor R wave progression	135 (19.5%)
ST changes non-specific	117 (18.7%)
Sinus tachycardia	122 (17.6%)
T wave abnormal NOS	113 (16.1%)
Myocardial infarction septal old	83 (12.7%)
Incomplete bundle branch block	85 (12.5%)
Ectopic atrial beats NOS	77 (10.8%)
Indeterminate axis EKG	66 (9.2%)
Left axis deviation EKG	64 (9.2%)
Right axis deviation EKG	62 (9.0%)
Left atrial hypertrophy (P mitrale)	59 (8.9%)
Low ventricular voltage NOS	57 (8.0%)
Left anterior hemiblock	52 (7.8%)
Left ventricular hypertrophy	51 (7.2%)
Myocardial infarction inferior old	43 (6.3%)
First degree AV block	43 (6.2%)
Right bundle branch block	29 (4.3%)
Bradycardia NOS	29 (4.1%)
Decreased voltage EKG	26 (3.7%)
Ventricular hypertrophy NOS	25 (3.6%)
Tachycardia NOS	25 (3.5%)
Atrial fibrillation	24 (3.4%)
Right atrial hypertrophy (P pulmonale)	24 (3.4%)
Myocardial infarction lateral old	16 (2.2%)
Ectopic rhythm NOS	15 (2.1%)

Data Source: Section 15, [Table 15.20](#)

1. The n (%) are based on number of subjects with measurements taken, not necessarily all 723 subjects.

NOS=not otherwise specified

During study treatment, 697 subjects (96.4%) had at least one new abnormality in ECG noted. The most commonly noted changes were an increase in the QT interval. However, an increase in QT interval was reported as an adverse experience for only three

subjects (see details following [Table 38](#)) and these experiences were not considered by the Investigator to be related to study treatment.

Details of all ECG changes reported as an adverse experience are shown in [Table 40](#).

Table 40 Number (%) Subjects Reporting ECG Changes as Adverse Experiences

Adverse Experience	Related to study drug	
	n (%)	n (%)
Tachycardia	24 (3.3%)	1 (0.1%)
Extrasystoles	17 (2.4%)	6 (0.8%)
Atrial fibrillation	14 (1.9%)	1 (0.1%)
Supraventricular extrasystoles	12 (1.7%)	6 (0.8%)
Bradycardia	12 (1.7%)	3 (0.4%)
Arrhythmia	7 (1.0%)	0
Bundle branch block	6 (0.8%)	0
Atrial arrhythmia	5 (0.7%)	0
ECG abnormal	5 (0.7%)	0
Palpitation	4 (0.6%)	1 (0.1%)
QT increased	3 (0.4%)	0
Atrioventricular block	2 (0.3%)	0
ECG abnormal specific	2 (0.3%)	0
Cardiac arrest	1 (0.1%)	0
Supraventricular tachycardia	1 (0.1%)	0
Ventricular fibrillation	1 (0.1%)	0
Ventricular arrhythmia	1 (0.1%)	0

Source Data: Section 15, [Table 15.3](#)

A total of 91 subjects (12.6%) had ECG changes reported as adverse experiences. Few of these adverse experiences were considered by the Investigator to be drug-related.

7.10. Safety Conclusions

In this long-term study, almost all subjects reported at least one adverse experience during treatment; these were reported by 93.6% of subjects. The majority of on-therapy adverse experiences were of mild or moderate intensity. The most common adverse experiences related to the respiratory, gastrointestinal, and body as a whole systems. The most frequently reported individual adverse experience was chronic obstructive airways disease (i.e., COPD exacerbation). The other most frequently reported adverse experiences were abdominal pain, diarrhoea and injury. Gastrointestinal adverse experiences (abdominal pain, diarrhoea, nausea, dyspepsia) and headache occurred at a higher percentage in subjects who had previously taken placebo in studies 042 and 091. Adverse experiences that were considered to be at least possibly study drug-related were reported by 27.1% of subjects, with abdominal pain, diarrhoea and nausea the most common.

In total, 123 subjects (17.0%) were withdrawn from this long-term study due to an adverse experience. Of these, 47 subjects were withdrawn due to adverse experiences that were considered by the Investigator to be drug-related. The most frequent reasons for withdrawal were abdominal pain, COPD exacerbation, nausea and pulmonary carcinoma. Apart from pulmonary carcinoma, the incidences of these and most other adverse experiences leading to subject withdrawal were greater in the group of subjects previously treated with placebo.

Fifteen subjects died of events starting during the on-therapy study treatment period and 9 subjects died of events starting during the post-therapy period. None of the deaths was considered by the Investigator to be related to study medication. The cause of death in the majority of cases was related to the respiratory or cardiovascular system.

There were 203 subjects (28.1%) who experienced on-therapy serious adverse experiences. The most frequently occurring on-therapy serious adverse experiences were chronic obstructive airways disease (i.e. COPD exacerbation), pneumonia and injury. Six subjects (four in the prior placebo treatment group and two in the prior SB-207499 treatment group) had serious adverse experiences that were considered by the Investigator to be possibly (suspected) related to study medication. Two subjects experienced GI haemorrhage, one subject experienced abdominal pain, diarrhoea and vomiting, one subject had abdominal pain, one subject experienced atrial fibrillation and one subject had a neoplasm (intestinal polyp). Of the 203 subjects with serious adverse experiences during the on-therapy period, 61 were withdrawn from the study as a result.

During treatment with study medication, 97 subjects (13.4%) experienced 151 gastrointestinal adverse experiences (GIAEs) of concern. The two most common GIAEs were abdominal pain and diarrhoea. GIAEs of concern occurred in a higher percentage of subjects who previously received placebo. One hundred and nine (59.6%) of the GIAEs were considered to be related (suspected or probable) to study medication by the Investigator. Thirty-three subjects (4.6%) were withdrawn because of GIAEs of concern.

Routine faecal occult blood testing resulted in a positive result for 35 subjects (5.7%). A total of 14 subjects were shown to have blood in faeces in association with a GIAE of concern (either by faecal occult blood testing and/or by overt blood on stool inspection). Faecal occult blood testing revealed four subjects with a positive faecal occult blood test result on-therapy and one further subject had a positive faecal occult blood test result at the safety follow-up visit after withdrawing for a GI haemorrhage. Stool assessment at the time of a GIAE showed that 11 subjects had blood in their stool and the faecal occult blood tests at the time of the GIAE of concern were positive for two of these subjects. Five of these subjects reported melaena, three reported GI haemorrhage, one reported bloody diarrhoea, one reported haemorrhoids and one reported dyspepsia. For four of these subjects the reported experiences were suspected by the investigator to be study drug-related; three of these subjects reported black, tarry stools and one subject had normal stool with red blood on the outside (the reported adverse experience was dyspepsia). The majority of subjects continued treatment with SB-207499; only three subjects were withdrawn because of these events whilst one further subject withdrew due to nausea, diarrhoea and vomiting which coexisted with an adverse experience of melaena. Of those subjects who continued in the study, none suffered a reoccurrence of a

GIAE event and none experienced a further positive faecal occult blood test result at any of the routine annual tests.

Eleven of the 14 subjects who showed signs of blood in their stools in association with a GIAE of concern had further tests to explore the cause of this bleeding. Seven subjects had colonoscopies and four had upper digestive endoscopies/gastroscopy. Results of these investigations did not reveal any sinister pathology.

In summary, the intensive gastrointestinal monitoring performed in this study has not identified any new, serious, potentially drug related effects of long-term treatment with SB-207499 on the gastrointestinal tract. In addition, the results of this final analysis show no substantial differences to those of the interim report [[GSK Document Number SB-207499/RSD-1017MT/1](#)]. There was no evidence for a treatment effect of SB-207499 on faecal occult blood results or clinically important changes in orthostatic vital signs in subjects experiencing GIAEs of concern. Although some changes were seen during treatment, faecal occult blood testing and orthostatic vital signs assessments did not reveal any evidence for acute or chronic blood loss associated with long-term treatment with SB-207499. Only one subject who was assessed to have blood in their stool had haemoglobin values that were of potential clinical concern. This subject, who had black, tarry stools, was withdrawn from the study because of this event.

Overall, mean changes from baseline in haematological and clinical chemistry laboratory values were small, and the percentage of subjects with laboratory values of potential clinical concern was low. There was no evidence for an adverse effect of SB-207499 on laboratory parameters.

The percentages of subjects with transitions in sitting vital signs from normal at baseline to values of potential clinical concern on-therapy were low and there was no evidence for an adverse effect on vital signs following long-term treatment with SB-207499.

Mean changes from baseline in ECG parameters were small. Transitions to high or low values for ECG parameters at any one point during the study were not uncommon. The most common transition was in absolute QTc values, however, the mean change from baseline in QTc was small. The most frequently occurring new-onset ECG abnormalities were an increase in QT interval, premature ventricular contractions NOS and sinus bradycardia. Overall, intensive 12-lead ECG monitoring did not raise any concerns about the cardiac safety of SB-207499.

8. EFFICACY RESULTS

Efficacy was the secondary objective of this study and therefore no primary efficacy variable was defined. The efficacy analysis focused on the within-group change from the baseline assessment of study 042 or study 091. No comparisons between the two groups were performed. In contrast to the safety data tables, data tables for efficacy showing change from baseline include on treatment data from the feeder studies 042 and 091. Week 24 data represents the end of these double-blind studies, although the treatment period in study 091 was 26 weeks (the final two weeks of this study were considered to be a run-out phase and these data were not included in any tables). An additional efficacy analysis was the within-group change from Visit 1 of study 040 for subjects randomised to placebo in study 042 or study 091. The Visit 1 data was equivalent to Week 24 data from study 042 and Week 26 data from study 091.

This was a long term safety study and consequently no primary efficacy variable was defined. Efficacy analyses have concentrated on a within-group change from the baseline assessment of the relevant feeder study (042 or 091). For subjects randomised to placebo in study 042 or study 091 a second analysis has looked at change from Visit 1 of study 040. No comparisons between the two groups were performed.

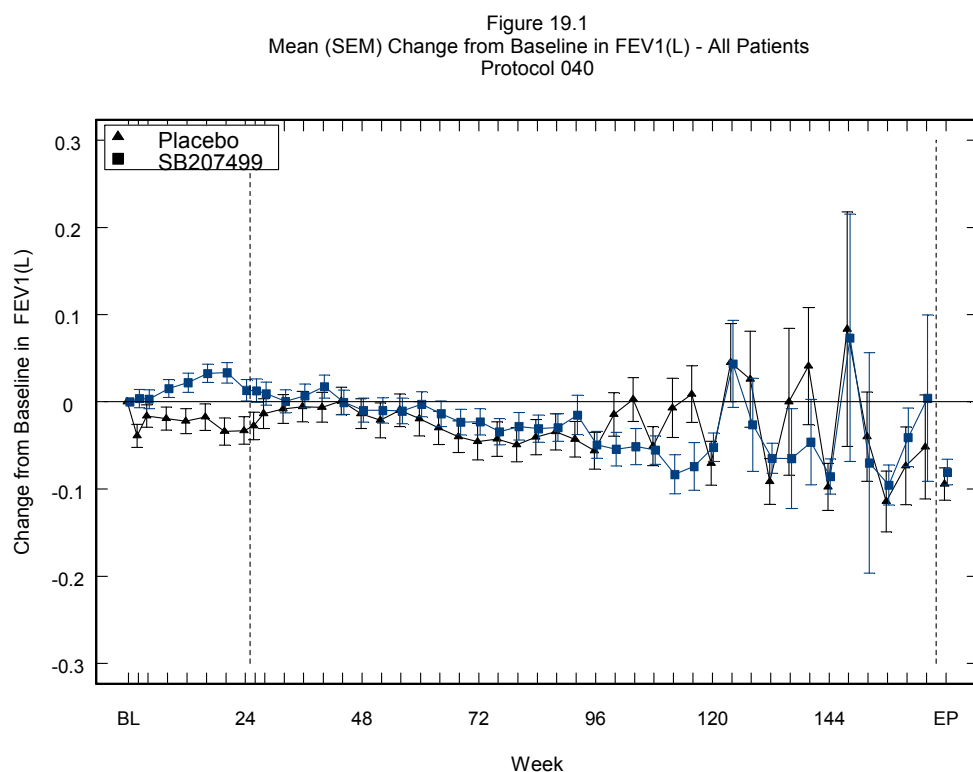
8.1. Pulmonary Function Tests

The mean changes from baseline of study 042 or study 091 in clinic trough pulmonary function parameters, FEV₁, FVC, PEFR, FEF₂₅₋₇₅, FEF₇₅, and FEV₆, and mean changes from Visit 1 in study 040 for FEV₁, FVC and PEFR for subjects randomised to placebo in studies 042 and 091 are shown in Section 14, [Table 14.1A](#), [Table 14.1B](#), [Table 14.2A](#), [Table 14.2B](#), [Table 14.3A](#), [Table 14.3B](#), [Table 14.4A](#), [Table 14.5A](#) and [Table 14.6A](#). The mean changes from baseline in pulmonary function tests are shown graphically in Section 19, [Figure 19.1](#) to [Figure 19.6](#) inclusive.

The changes from baseline at Week 24 are discussed first, representing the end of study 042 or 091. At subsequent assessment points, all subjects were receiving SB-207499. This is followed by a discussion of the changes from baseline during treatment with SB-207499 over the course of study 040.

8.1.1. FEV₁

Changes from baseline in FEV₁ data are displayed graphically in [Figure 1](#) (data source Section 19, [Figure 19.1](#)) and summarised in [Table 41](#).

Figure 1 Mean (SEM) Change from Baseline in FEV₁ (L) – All Subjects**Table 41 Changes from Baseline in FEV₁ (L)**

Week of Treatment	Prior Treatment	n	mean	sd	mean change from baseline	sd	95% CI
Baseline ¹	Placebo	232	1.45	0.44			
	SB-207499	469	1.48	0.46			
Week 24 ²	Placebo	231	1.41	0.47	-0.03	0.24	-0.06, -0.00
	SB-207499	468	1.49	0.51	0.01	0.26	-0.01, 0.04
Week 52	Placebo	188	1.43	0.49	-0.02	0.28	-0.06, 0.02
	SB-207499	419	1.47	0.54	-0.01	0.30	-0.04, 0.02
Week 104	Placebo	98	1.40	0.53	0.00	0.25	-0.05, 0.05
	SB-207499	191	1.37	0.47	-0.05	0.29	-0.09, -0.01
Week 144	Placebo	130	1.36	0.54	-0.10	0.31	-0.15, -0.04
	SB-207499	278	1.41	0.54	-0.09	0.34	-0.13, -0.05
Week 156	Placebo	96	1.35	0.57	-0.11	0.34	-0.18, -0.04
	SB-207499	199	1.36	0.50	-0.10	0.32	-0.14, -0.05
Endpoint ³	Placebo	232	1.35	0.46	-0.09	0.28	-0.13, -0.06
	SB-207499	469	1.40	0.50	-0.08	0.31	-0.11, -0.05

Source data: Section 14, [Table 14.1A](#)

1. Baseline refers to the start of study 042 or study 091, and the week numbers are relative to baseline of study 042 or study 091.
2. Week 24 represents the end of study 042 or study 091. All subjects received SB-207499 at subsequent assessments.
3. Endpoint refers to last value reported on therapy.

The mean FEV₁ at baseline of study 042 and study 091 was 1.45 L for subjects randomised to placebo and 1.48 L for subjects randomised to SB-207499. By Week 24, at the end of studies 042 and 091, the FEV₁ had decreased from baseline by a mean of 30 mL in the placebo group and increased from baseline by a mean of 10 mL in the SB-207499 group.

From Week 24 (the start of study 040), mean FEV₁ initially showed only small changes from baseline (start of study 042 or study 091) in both groups with a small increase in mean FEV₁ for subjects switching from placebo and a reduction in the 30 mL decrease from baseline in subjects continuing with SB-207499. Subjects in the prior placebo group showed a mean decrease in FEV₁ of 20 mL at Week 52 and subjects continuing with SB-207499 showed a 10 mL decrease in mean FEV₁ at this timepoint. Subsequent mean reductions from baseline of 30 to 60 mL in subjects switching from placebo were seen during Weeks 64 to 96, and of 30 to 90 mL in subjects continuing with SB-207499 were seen during Weeks 76 to 144. At endpoint, FEV₁ had decreased by a mean of 90 mL in the prior placebo group and by 80 mL in the prior SB-207499 group as compared with baseline values of study 042 or study 091.

Subjects switching from placebo to SB-207499 at the start of study 040 generally showed an increase in mean FEV₁ at the start of study 040 as shown in Section 14, [Table 14.1B](#) and summarised in [Table 42](#).

Table 42 **Changes (L) from Visit 1 in FEV₁ in Subjects Randomised to Placebo in Studies 042 and 091**

Week ² of Treatment	n	mean	sd	mean change from baseline	sd	95% CI
Day 1 ¹	232	1.42	0.47			
Week 4	218	1.43	0.49	0.02	0.18	-0.01, 0.04
Week 12	206	1.44	0.49	0.02	0.19	-0.01, 0.05
Week 24	191	1.44	0.49	0.01	0.19	-0.02, 0.04
Week 52	180	1.41	0.51	-0.02	0.22	-0.05, 0.01
Week 108	144	1.36	0.54	-0.07	0.25	-0.11, -0.03
Week 120	130	1.36	0.54	-0.08	0.24	-0.12, -0.04
Week 132	96	1.35	0.57	-0.13	0.28	-0.18, -0.07
Endpoint ³	232	1.35	0.46	-0.07	0.24	-0.10, -0.04

Data Source: Section 14, [Table 14.1B](#)

1. Day 1 is the baseline of study 040 and uses data from Week 24 of study 042 and Week 26 of study 091.
2. The week number is relative to the start of study 040.
3. Endpoint refers to last value reported on therapy.

Subjects showed an initial mean increase of in FEV₁ relative to baseline of study 040 which was maintained until around Week 36.

8.1.2. FVC

The changes from baseline in FVC are shown in Section 14, [Table 14.2A](#) and Section 19, [Figure 19.2](#) and summarised in [Table 43](#).

Table 43 Changes from Baseline in FVC (L)

Week of Treatment	Prior Treatment	n	mean	sd	mean change from baseline	sd	95% CI
Baseline ¹	Placebo	232	2.81	0.75			
	SB-207499	469	2.81	0.76			
Week 24 ²	Placebo	231	2.76	0.76	-0.05	0.38	-0.10, -0.00
	SB-207499	468	2.82	0.78	0.01	0.40	-0.03, 0.05
Week 52	Placebo	188	2.78	0.76	-0.04	0.44	-0.11, 0.02
	SB-207499	419	2.81	0.79	-0.01	0.43	-0.05, 0.04
Week 104	Placebo	98	2.77	0.80	0.01	0.50	-0.08, 0.11
	SB-207499	191	2.68	0.74	-0.06	0.44	-0.13, 0.00
Week 144	Placebo	130	2.67	0.77	-0.13	0.53	-0.22, -0.03
	SB-207499	278	2.68	0.78	-0.09	0.47	-0.15, -0.04
Week 156	Placebo	96	2.70	0.79	-0.17	0.55	-0.28, -0.06
	SB-207499	199	2.62	0.75	-0.11	0.51	-0.18, -0.04
Endpoint ³	Placebo	232	2.69	0.72	-0.13	0.50	-0.19, -0.06
	SB-207499	469	2.73	0.78	-0.08	0.50	-0.12, -0.03

Source data: Section 14, [Table 14.2A](#)

1. Baseline refers to the start of study 042 or study 091, and the week numbers are relative to baseline of study 042 or study 091.
2. Week 24 represents the end of study 042 or study 091. All subjects received SB-207499 at subsequent assessments.
3. Endpoint refers to last value reported on therapy.

Results for FVC showed a similar pattern to those for FEV₁. During studies 042 and 091 (up to Week 24) FVC had decreased by a mean of 50 mL in the placebo group and increased by 10 mL in the SB-207499 group.

From Week 24, mean FVC tended initially to show smaller reductions from baseline (start of study 042 or study 091) in the prior placebo group. Subjects switching from placebo to SB-207499 at the start of study 040 showed a mean reduction in FVC at Week 52 of 40 mL, smaller than the decrease that had been seen up to Week 24. Subjects continuing with SB-207499 showed a 10 mL decrease in mean FVC at the Week 52 timepoint, the same as at Week 24. Beyond Week 96, larger decreases from baseline were seen in both groups and at endpoint, FVC had a mean reduction from baseline of 130 mL in the prior placebo group compared with a slightly smaller reduction of 80 mL in the prior SB-207499 group.

As for FEV₁, subjects switching from placebo to SB-207499 at the start of study 040 generally showed an increase in mean FVC at the start of study 040 as shown in Section 14, [Table 14.2B](#) and summarised in [Table 44](#).

Table 44 Changes (L) from Visit 1 in FVC in Subjects Randomised to Placebo in Studies 042 and 091

Week ² of Treatment	n	mean	sd	mean change from baseline	sd	95% CI
Day 1 ¹	232	2.76	0.76			
Week 4	218	2.79	0.80	0.04	0.32	-0.00, 0.08
Week 12	206	2.78	0.78	0.03	0.33	-0.01, 0.08
Week 24	191	2.81	0.79	0.03	0.31	-0.01, 0.08
Week 52	180	2.78	0.77	-0.01	0.34	-0.06, 0.04
Week 108	144	2.66	0.74	-0.11	0.44	-0.18, -0.03
Week 120	130	2.67	0.77	-0.09	0.46	-0.17, -0.01
Week 132	96	2.70	0.79	-0.18	0.48	-0.28, -0.08
Endpoint ³	232	2.69	0.72	-0.07	0.45	-0.13, -0.02

Data Source: Section 14, [Table 14.2B](#)

1. Day 1 is the baseline of study 040 and uses data from Week 24 of study 042 and Week 26 of study 091.
2. The week number is relative to the start of study 040.
3. Endpoint refers to last value reported on therapy.

8.1.3. PEFR

The changes from baseline in PEFR are shown in Section 14, [Table 14.3A](#) and Section 19, [Figure 19.3](#) and summarised in [Table 45](#).

Table 45 Changes from Baseline in PEFR (L/min)

Week of Treatment	Prior Treatment	n	mean	sd	mean change from baseline	sd	95% CI
Baseline ¹	Placebo	232	200.1	73.3			
	SB-207499	469	204.7	74.8			
Week 24 ²	Placebo	231	199.3	75.6	-1.1	42.0	-6.6, 4.3
	SB-207499	468	206.7	77.7	1.9	47.2	-2.4, 6.2
Week 52	Placebo	188	204.4	76.3	3.1	44.6	-3.3, 9.5
	SB-207499	419	208.9	82.8	3.6	57.2	-1.9, 9.1
Week 104	Placebo	98	201.3	83.9	5.6	50.9	-4.7, 15.8
	SB-207499	191	194.6	73.5	-3.3	59.3	-11.8, 5.2
Week 144	Placebo	129	200.6	84.1	-0.1	50.7	-8.9, 8.7
	SB-207499	278	202.6	82.7	-2.1	59.4	-9.1, 4.9
Week 156	Placebo	96	196.6	85.3	-5.3	58.9	-17.2, 6.7
	SB-207499	198	199.7	85.1	-1.6	65.2	-10.7, 7.5
Endpoint ³	Placebo	232	195.1	75.3	-5.0	49.0	-11.3, 1.4
	SB-207499	469	201.3	78.1	-3.4	57.9	-8.7, 1.8

Source data: Section 14, [Table 14.3A](#)

1. Baseline refers to the start of study 042 or study 091, and the week numbers are relative to baseline of study 042 or study 091.
2. Week 24 represents the end of study 042 or study 091. All subjects received SB-207499 at subsequent assessments.
3. Endpoint refers to last value reported on therapy.

Only small changes were seen in PEFR at all timepoints. As for FEV₁ and FVC, subjects switching from placebo to SB-207499 at the start of study 040 generally showed an

increase in mean PEFR at the start of study 040 as shown in Section 14, [Table 14.3B](#) and summarised in Table 46.

Table 46 Changes (L/min) from Visit 1 in PEFR in Subjects Randomised to Placebo in Studies 042 and 091

Week ² of Treatment	n	mean	sd	mean change from baseline	sd	95% CI
Day 1 ¹	232	202.4	77.6			
Week 4	218	204.1	75.2	2.4	31.3	-1.7, 6.6
Week 12	205	203.9	76.7	1.1	33.2	-3.5, 5.7
Week 24	191	204.9	80.1	-0.3	35.0	-5.3, 4.7
Week 52	180	203.0	78.9	-3.9	33.6	-8.8, 1.1
Week 108	144	200.4	81.7	-6.5	39.0	-12.9, -0.1
Week 120	129	200.6	84.1	-7.7	37.4	-14.2, -1.2
Week 132	96	196.6	85.3	-17.3	40.7	-25.6, -9.1
Endpoint ³	232	195.1	75.3	-7.2	38.1	-12.2, -2.3

Data Source: Section 14, [Table 14.3B](#)

1. Day 1 is the baseline of study 040 and uses data from Week 24 of study 042 and Week 26 of study 091.
2. The week number is relative to the start of study 040.
3. Endpoint refers to last value reported on therapy.

8.1.4. Other Pulmonary Function Tests (FEF₂₅₋₇₅, FEF₇₅, and FEV₆)

The changes from baseline in FEF₂₅₋₇₅, FEF₇₅, and FEV₆ are shown in Section 14, [Table 14.4A](#), [14.5A](#) and [14.6A](#), respectively, and are shown graphically in Section 19, [Figure 19.4](#), [Figure 19.5](#) and [Figure 19.6](#), respectively. The results are summarised in [Table 47](#), [Table 48](#) and [Table 49](#). For all variables, small decreases were seen through the study.

Table 47 Changes from Baseline in FEF₂₅₋₇₅ (L/sec)

Week of Treatment	Prior Treatment	n	mean	sd	mean change from baseline	sd	95% CI
Baseline ¹	Placebo	232	0.67	0.34			
	SB-207499	469	0.72	0.41			
Week 24 ²	Placebo	231	0.65	0.37	-0.02	0.21	-0.05, 0.01
	SB-207499	467	0.73	0.45	0.01	0.27	-0.02, 0.03
Week 52	Placebo	188	0.67	0.41	-0.01	0.25	-0.04, 0.03
	SB-207499	417	0.72	0.49	-0.01	0.31	-0.03, 0.02
Week 108	Placebo	162	0.65	0.42	-0.04	0.27	-0.08, 0.00
	SB-207499	333	0.70	0.46	-0.03	0.28	-0.07, -0.00
Week 144	Placebo	129	0.63	0.41	-0.06	0.27	-0.11, -0.02
	SB-207499	278	0.69	0.47	-0.06	0.31	-0.10, -0.02
Week 156	Placebo	95	0.61	0.45	-0.07	0.29	-0.13, -0.01
	SB-207499	197	0.64	0.40	-0.07	0.28	-0.11, -0.03
Endpoint ³	Placebo	232	0.61	0.34	-0.06	0.23	-0.09, -0.03
	SB-207499	469	0.66	0.43	-0.06	0.30	-0.09, -0.03

Data source: Section 14, [Table 14.4A](#)

1. Baseline refers to the start of study 042 or study 091, and the week numbers are relative to baseline of study 042 or study 091.
2. Week 24 represents the end of study 042 or study 091. All subjects received SB-207499 at subsequent assessments.
3. Endpoint refers to last value reported on therapy.

Table 48 Changes from Baseline in FEF₇₅ (L/sec)

Week of Treatment	Prior Treatment	n	mean	sd	mean change from baseline	sd	95% CI
Baseline ^a	Placebo	232	0.32	0.21			
	SB-207499	469	0.35	0.30			
Week 24 ^b	Placebo	231	0.30	0.17	-0.02	0.14	-0.04, -0.01
	SB-207499	468	0.34	0.31	-0.02	0.31	-0.04, 0.01
Week 52	Placebo	188	0.31	0.22	-0.02	0.19	-0.04, 0.01
	SB-207499	417	0.33	0.24	-0.03	0.24	-0.05, -0.00
Week 108	Placebo	161	0.30	0.20	-0.03	0.18	-0.06, -0.00
	SB-207499	331	0.32	0.23	-0.04	0.27	-0.07, -0.01
Week 144	Placebo	129	0.29	0.18	-0.05	0.19	-0.08, -0.01
	SB-207499	276	0.31	0.24	-0.04	0.17	-0.06, -0.02
Week 156	Placebo	93	0.29	0.30	-0.05	0.25	-0.10, 0.00
	SB-207499	195	0.32	0.42	-0.02	0.38	-0.07, 0.04
Endpoint ^c	Placebo	232	0.28	0.17	-0.04	0.19	-0.06, -0.01
	SB-207499	469	0.32	0.38	-0.03	0.36	-0.067 0.00

1. a. Baseline refers to the start of study 042 or study 091, and the week numbers are relative to baseline of study 042 or study 091.
2. b. Week 24 represents the end of study 042 or study 091. All subjects received SB-207499 at subsequent assessments.
- c. Endpoint refers to last value reported on therapy.

Data source: Section 14, [Table 14.5A](#)

Table 49 Changes from Baseline in FEV₆ (L)

Week of Treatment	Prior Treatment	n	mean	sd	mean change from baseline	sd	95% CI
Baseline ¹	Placebo	163	2.59	0.66			
	SB-207499	311	2.55	0.65			
Week 24 ²	Placebo	147	2.52	0.65	-0.07	0.29	-0.12, -0.02
	SB-207499	283	2.53	0.64	0.02	0.31	-0.02, 0.05
Week 52	Placebo	114	2.56	0.69	-0.05	0.36	-0.11, 0.02
	SB-207499	243	2.51	0.67	-0.02	0.30	-0.06, 0.01
Week 108	Placebo	93	2.49	0.62	-0.12	0.39	-0.20, -0.04
	SB-207499	195	2.48	0.62	-0.06	0.33	-0.10, -0.01
Week 144	Placebo	76	2.42	0.62	-0.19	0.42	-0.28, -0.09
	SB-207499	164	2.40	0.64	-0.12	0.32	-0.16, -0.07
Week 156	Placebo	60	2.48	0.73	-0.22	0.52	-0.35, -0.08
	SB-207499	117	2.36	0.61	-0.10	0.33	-0.16, -0.04
Endpoint ³	Placebo	163	2.46	0.67	-0.13	0.42	-0.20, -0.07
	SB-207499	311	2.45	0.66	-0.10	0.35	-0.14, -0.06

Data source: Section 14, [Table 14.6A](#)

1. Baseline refers to the start of study 042 or study 091, and the week numbers are relative to baseline of study 042 or study 091.
2. Week 24 represents the end of study 042 or study 091. All subjects received SB-207499 at subsequent assessments.
3. Endpoint refers to last value reported on therapy.

8.2. Overall and Post-Exercise Breathlessness

The mean changes from baseline in the overall and post-exercise breathlessness scores as measured by the Modified Borg scale are shown for all subjects in Section 14, [Table 14.11A](#) and [Table 14.12A](#), respectively, and are presented graphically in Section 19, [Figure 19.11](#) and [Figure 19.12](#), respectively. The mean changes from Day 1 of study 040 for subjects who were randomised to placebo in study 042 or study 091 are shown in Section 14, [Table 14.11B](#) and [Table 14.12B](#).

The results are summarised in [Table 50](#).

Table 50 **Changes from Baseline in Breathlessness**

Week of Treatment	Prior Treatment	n	mean	sd	mean change from baseline	sd	95% CI
Overall breathlessness at rest							
Baseline ¹	Placebo	235	3.18	1.28			
	SB-207499	470	3.19	1.49			
Week 24 ²	Placebo	235	2.88	1.46	-0.30	1.43	-0.48, -0.12
	SB-207499	470	2.86	1.51	-0.33	1.45	-0.46, -0.20
Week 52	Placebo	191	3.08	1.62	-0.13	1.51	-0.34, 0.09
	SB-207499	422	2.94	1.52	-0.24	1.47	-0.38, -0.10
Week 108	Placebo	163	2.99	1.54	-0.20	1.61	-0.45, 0.05
	SB-207499	336	2.87	1.57	-0.26	1.59	-0.43, -0.09
Week 144	Placebo	132	3.25	1.71	0.00	1.82	-0.31, 0.31
	SB-207499	283	2.93	1.71	-0.14	1.68	-0.34, 0.06
Week 156	Placebo	99	3.30	1.61	0.16	1.69	-0.18, 0.50
	SB-207499	201	3.09	1.73	-0.01	1.71	-0.25, 0.23
Endpoint ³	Placebo	235	3.21	1.61	0.02	1.60	-0.18, 0.23
	SB-207499	470	3.00	1.77	-0.19	1.67	-0.34, -0.04
Breathlessness after exercise							
Baseline ¹	Placebo	208	3.67	1.68			
	SB-207499	439	3.82	1.83			
Week 24 ²	Placebo	206	3.48	1.73	-0.17	1.33	-0.36, 0.01
	SB-207499	436	3.40	1.71	-0.41	1.52	-0.56, -0.27
Week 48	Placebo	176	3.45	1.64	-0.25	1.58	-0.48, -0.01
	SB-207499	405	3.45	1.72	-0.35	1.72	-0.52, -0.18
Week 108	Placebo	145	3.59	1.77	-0.11	1.90	-0.42, 0.21
	SB-207499	307	3.54	1.81	-0.29	1.92	-0.51, -0.08
Week 144	Placebo	117	3.77	1.72	0.06	2.09	-0.32, 0.44
	SB-207499	254	3.50	1.88	-0.21	1.99	-0.45, 0.04
Week 156	Placebo	86	4.05	1.79	0.52	2.16	0.05, 0.98
	SB-207499	185	3.64	1.83	-0.04	1.91	-0.32, 0.23
Endpoint ³	Placebo	208	3.95	1.86	0.28	1.83	0.03, 0.53
	SB-207499	439	3.60	1.92	-0.22	1.97	-0.40, -0.03

Source data: Section 14, [Table 14.11A](#) and [Table 14.12A](#)

1. Baseline refers to the start of study 042 or study 091, and the week numbers are relative to baseline of study 042 or study 091.
2. Week 24 represents the end of study 042 or study 091. All subjects received SB-207499 at subsequent assessments.
3. Endpoint refers to last value reported on therapy.

Improvements in breathlessness score were seen in the early part of the study in both treatment groups. At endpoint, the overall breathlessness score had decreased from baseline in the prior SB-207499 treatment group, indicating an improvement in breathlessness relative to baseline, but there was a increase in the prior placebo treatment group. Results for the post-exercise dyspnoea scores were similar.

Subjects switching from placebo to SB-207499 at the start of study 040 generally showed an increase in overall dyspnoea score at rest. Decreases were seen only at two timepoints: 2 weeks (-0.12) and 4 weeks (-0.03) after switching to SB-207499. For dyspnoea after exercise, decreases in score were seen after 12 weeks (-0.03) and 24 weeks (-0.01) of treatment with SB-207499. Breathlessness scores increased at all other timepoints. Results are summarised in [Table 51](#).

Table 51 Changes from Visit 1 in Breathlessness in Subjects Randomised to Placebo in Studies 042 and 091

Week ² of Treatment	n	mean	sd	mean change from baseline	sd	95% CI
Overall breathlessness at rest						
Day 1 ¹	234	2.87	1.46			
Week 4	217	2.85	1.35	-0.03	1.05	-0.17, 0.11
Week 12	207	2.91	1.39	0.02	1.09	-0.13, 0.17
Week 24	192	2.97	1.43	0.11	1.11	-0.05, 0.26
Week 48	183	2.96	1.44	0.09	1.20	-0.09, 0.26
Week 108	143	3.31	1.73	0.43	1.45	0.19, 0.67
Week 120	131	3.25	1.71	0.38	1.56	0.11, 0.65
Week 132	98	3.33	1.60	0.42	1.45	0.13, 0.71
Endpoint ³	234	3.21	1.61	0.34	1.32	0.17, 0.51
Breathlessness after exercise						
Day 1 ¹	205	3.47	1.71			
Week 12	198	3.46	1.65	-0.03	1.23	-0.20, 0.14
Week 24	174	3.42	1.62	-0.01	1.30	-0.20, 0.19
Week 48	166	3.45	1.59	0.01	1.43	-0.21, 0.23
Week 108	121	3.77	1.75	0.31	1.91	-0.03, 0.66
Week 120	116	3.77	1.73	0.43	1.81	0.09, 0.76
Week 132	86	4.05	1.79	0.64	1.92	0.23, 1.05
Endpoint ³	205	3.94	1.85	0.47	1.70	0.24, 0.70

Data Source: Section 14, [Table 14.11B](#) and [Table 14.12B](#)

1. Day 1 is the baseline of study 040 and uses data from Week 24 of study 042 and Week 26 of study 091.
2. The week number is relative to the start of study 040.
3. Endpoint refers to last value reported on therapy.

8.3. Exercise Tolerance Test

The mean change from baseline in exercise tolerance (i.e. the distance walked during a 6-minute walking period) is shown for all subjects in Section 14, [Table 14.13A](#) and is presented graphically in Section 19, [Figure 19.13](#). The mean change from Day 1 of study 040 for subjects who were randomised to placebo in study 042 and study 091 is shown in Section 14, [Table 14.13B](#).

Few differences from baseline in the distance walked in 6 minutes were seen. At Week 24 (end of double blind treatment) there was an increase seen for both treatment groups which was higher for subjects treated with placebo (15.7 m) than for those treated with SB-207499 (8.1 m). At endpoint in study 040, there was a decrease in the distance walked in subjects who had received prior SB-207499 treatment (-18.7 m) compared with an increase for those who had received prior placebo (7.4 m).

The results are summarised in [Table 52](#).

Table 52 Changes from Baseline in Distance Walked (m)

Week of Treatment	Prior Treatment	n	mean	sd	mean change from baseline	sd	95% CI
Baseline ¹	Placebo	207	411.3	138.2			
	SB-207499	441	435.0	143.1			
Week 24 ²	Placebo	205	428.1	137.0	15.7	90.2	3.3, 28.1
	SB-207499	438	443.4	131.8	8.1	90.7	-0.4, 16.6
Week 48	Placebo	178	425.5	141.5	7.8	94.7	-6.2, 21.8
	SB-207499	409	430.9	139.9	-7.1	96.7	-16.5, 2.3
Week 108	Placebo	146	421.7	131.1	9.2	118.3	-10.2, 28.5
	SB-207499	312	419.8	148.1	-7.9	129.1	-22.2, 6.5
Week 144	Placebo	118	414.3	143.6	10.9	116.5	-10.3, 32.2
	SB-207499	258	422.9	155.3	-7.3	136.6	-24.1, 9.4
Week 156	Placebo	86	416.2	148.3	5.3	133.3	-23.3, 33.9
	SB-207499	186	433.8	150.6	-10.0	116.5	-26.8, 6.9
Endpoint ³	Placebo	207	418.6	150.6	7.4	116.2	-8.5, 23.3
	SB-207499	441	416.3	150.7	-18.7	129.4	-30.8, -6.6

Source data: Section 14, [Table 14.13A](#)

1. Baseline refers to the start of study 042 or study 091, and the week numbers are relative to baseline of study 042 or study 091.
2. Week 24 represents the end of study 042 or study 091. All subjects received SB-207499 at subsequent assessments.
3. Endpoint refers to last value reported on therapy.

Subjects switching from placebo to SB-207499 at the start of study 040 showed a decrease in the distance walked in 6 minutes from the Visit 1 value. At endpoint, the decrease was 10.4 m (see [Table 53](#)).

Table 53 Changes from Visit 1 in Distance Walked (m) in Subjects Randomised to Placebo in Studies 042 and 091

Week ² of Treatment	n	mean	sd	mean change from baseline	sd	95% CI
Day 1 ¹	205	429.2	140.6			
Week 12	200	426.6	143.4	-4.7	103.8	-19.2, 9.8
Week 24	176	424.9	140.0	-11.4	105.3	-27.1, 4.2
Week 48	169	419.7	134.3	-19.5	103.5	-35.2, -3.8
Week 108	122	419.2	129.5	-1.3	121.3	-23.0, 20.5
Week 120	118	409.8	142.5	-5.8	128.9	-29.3, 17.7
Week 132	87	413.5	149.6	-22.8	144.0	-53.5, 7.9
Endpoint ³	205	418.8	147.3	-10.4	130.9	-28.4, 7.7

Data Source: Section 14, [Table 14.13B](#)

1. Day 1 is the baseline of study 040 and uses data from Week 24 of study 042 and Week 26 of study 091.
2. The week number is relative to the start of study 040.
3. Endpoint refers to last value reported on therapy.

8.4. COPD Exacerbations

COPD exacerbations during study 040 are presented in Section 14, [Table 14.24](#) and COPD exacerbation rates per subject year of follow-up are shown in Section 14, [Table 14.25](#).

The exacerbation rate per year in the prior placebo group (1.396; 95% CI 1.294, 1.507) was slightly higher than that in the prior SB-207499 group (1.307; 95% CI 1.238, 1.379). The number of subjects with COPD exacerbations was slightly higher in the prior SB-207499 group than in the prior placebo group. A total of 160 subjects (65.8%) in the prior placebo group and 334 subjects (69.6%) in the prior SB-207499 group experienced 658 and 1310 COPD exacerbations, respectively. No conclusions as to the effect of SB-207499 on exacerbations can be drawn due to the lack of an appropriate control group.

8.5. Efficacy Conclusions

Small decreases in lung function were seen in both prior treatment groups although these tended to be smaller in the prior SB-207499 group than in the prior placebo group. Subjects switched from placebo to SB-207499 at the start of study 040 showed improvements in lung function at the start of study 040.

Overall breathlessness scores decreased in both prior treatment groups during the study treatment period. There was a small decrease in the distance walked in 6 minutes in the prior SB-207499 group compared with a small increase in the prior placebo group.

The exacerbation rate was slightly lower in the prior SB-207499 group than in the prior placebo group. No conclusions as to the effect of SB-207499 on exacerbations can be drawn due to the lack of an appropriate control group.

9. HEALTH OUTCOMES RESULTS

9.1. Humanistic Outcomes

9.1.1. SGRQ

The mean change from baseline over time in the total SGRQ score and the symptoms, impacts, and activities scores of the SGRQ are shown for all subjects in Section 14, [Table 14.7A](#), [Table 14.8A](#), [Table 14.9A](#) and [Table 14.10A](#), respectively. The data are presented graphically in Section 19, [Figure 19.07](#), [Figure 19.08](#), [Figure 19.09](#) and [Figure 19.10](#), respectively. The mean changes from Day 1 of study 040 for subjects who were randomised to placebo in study 042 or study 091 are shown in Section 14, [Table 14.7B](#), [Table 14.8B](#), [Table 14.9B](#) and [Table 14.10B](#) for the SGRQ total score, symptoms score, impacts score and activities scores, respectively.

The baseline total SGRQ scores (42.5 for the prior placebo group and 42.3 for the prior SB-207499 group) indicated that subjects had impaired health status at baseline. The changes from baseline in total SGRQ are shown in [Figure 2](#) (data source Section 19, [Figure 19.7](#)) and changes in total score and domain scores are summarised in [Table 54](#).

Figure 2 Mean (SEM) Change from Baseline in SGRQ Total Score – All Subjects

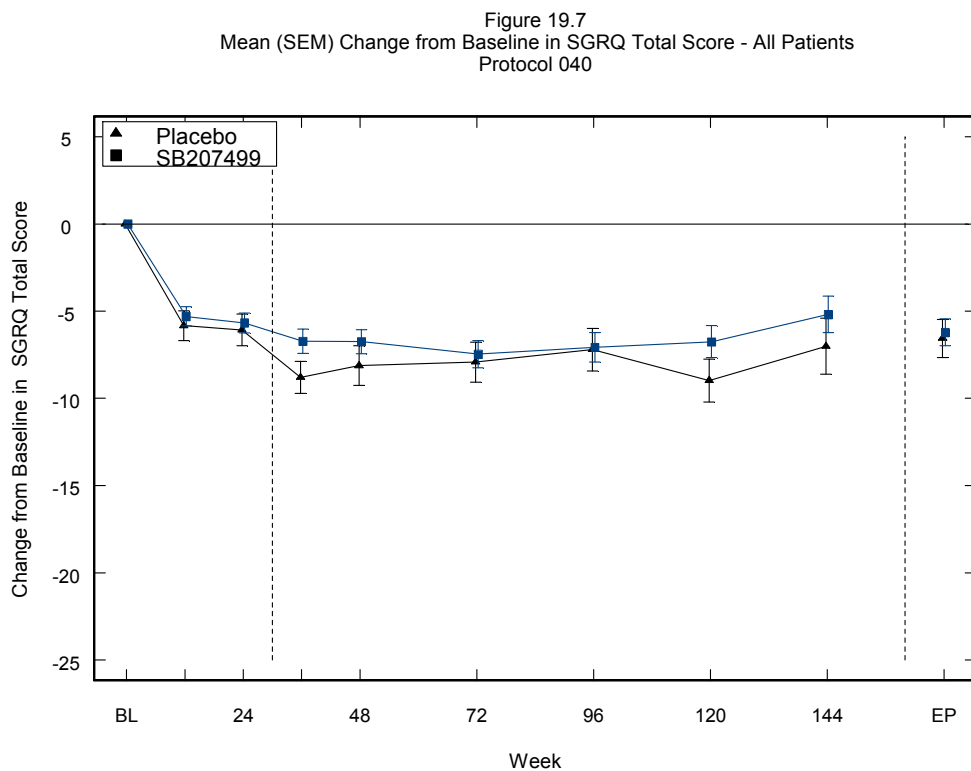


Table 54 Mean Change from Baseline in Total Score and Symptom, Impacts and Activities Subscales of SGRQ for All Subjects

			Assessment		Change from Baseline		
Week of Treatment	Prior Treatment Group	N	Mean	sd	Mean	sd	95%CI
Total Score							
Baseline ¹	Placebo	212	42.5	16.6			
	SB-207499	453	42.3	17.7			
Week 24 ²	Placebo	211	36.4	18.0	-6.1	13.2	-7.9, -4.3
	SB-207499	441	36.6	19.5	-5.7	12.0	-6.8, -4.5
Week 48	Placebo	184	35.1	18.4	-8.1	15.5	-10.4, -5.9
	SB-207499	401	35.1	19.4	-6.7	13.8	-8.1, -5.4
Week 144	Placebo	101	35.5	17.3	-7.0	16.1	-10.2, -3.8
	SB-207499	218	34.6	19.2	-5.2	15.4	-7.2, -3.1
Endpoint ³	Placebo	212	36.0	18.9	-6.6	16.0	-8.7, -4.4
	SB-207499	453	36.1	21.2	-6.2	16.2	-7.7, -4.7
Symptoms Score							
Baseline ¹	Placebo	214	53.0	21.3			
	SB-207499	457	51.9	22.6			
Week 24 ²	Placebo	213	41.9	23.1	-11.0	22.6	-14.0, -7.9
	SB-207499	451	41.5	24.5	-10.3	20.0	-12.1, -8.4
Week 144	Placebo	105	39.1	21.8	-12.5	24.9	-17.3, -7.6
	SB-207499	227	35.5	23.2	-12.2	22.9	-15.2, -9.2
Endpoint ³	Placebo	214	39.2	24.1	-13.8	24.4	-17.0, -10.5
	SB-207499	457	38.0	24.9	-13.9	23.4	-16.1, -11.8
Impacts Score							
Baseline ¹	Placebo	212	31.8	18.0			
	SB-207499	453	31.5	19.2			
Week 24 ²	Placebo	211	26.7	18.6	-5.1	14.5	-7.1, -3.1
	SB-207499	441	26.7	20.4	-4.8	14.1	-6.1, -3.5
Week 144	Placebo	101	26.3	19.5	-5.9	18.3	-9.5, -2.3
	SB-207499	218	26.0	20.0	-3.7	17.8	-6.1, -1.3
Endpoint ³	Placebo	212	26.8	19.8	-5.0	18.0	-7.4, -2.5
	SB-207499	453	26.8	21.5	-4.7	17.9	-6.3, -3.0
Activities Score							
Baseline ¹	Placebo	212	55.4	19.9			
	SB-207499	453	55.6	21.0			
Week 24 ²	Placebo	211	50.6	22.2	-4.7	15.7	-6.9, -2.6
	SB-207499	441	51.3	22.9	-4.2	14.9	-5.6, -2.8
Week 144	Placebo	101	49.9	20.1	-5.1	18.6	-8.7, -1.4
	SB-207499	218	49.7	24.1	-3.3	18.8	-5.8, -0.8
Endpoint ³	Placebo	212	50.4	22.4	-5.0	17.1	-7.3, -2.7
	SB-207499	453	51.4	25.4	-4.2	20.2	-6.0, -2.3

Data Source: Section 14, [Table 14.7A](#), [Table 14.8A](#), [Table 14.9A](#), [Table 14.10A](#)

1. Baseline refers to the start of studies 042 and 091 and the week numbers are relative to baseline of these studies. Only data from subjects continuing into study 040 are included.
2. Week 24 represents the end of study 042 or study 091. All subjects received SB-207499 at subsequent assessments.
3. Endpoint refers to last value reported on therapy.

At the end of studies 042 and 091 (Week 24) there were decreases in the SGRQ total score (i.e. improvements in health status) in both treatment groups: -6.1 for placebo and -5.7 for SB-207499. At the start of study 040, subjects previously receiving placebo showed further decreases in score from baseline at Weeks 36 to 120 but by Week 144 both groups had improvements of a similar size to those at the start of study 040. At endpoint there were decreases in the SGRQ total score of -6.6 for the prior placebo group and -6.2 for the prior SB-207499 group. A similar pattern was seen for the symptoms, activities and impacts scores: further improvement from baseline for the prior placebo group at entry to study 040, but improvements at endpoint of similar magnitude in both prior treatment groups. The mean changes in SGRQ from Day 1 of study 040 for subjects who were randomised to placebo in study 042 or study 091 are summarised in [Table 55](#).

Table 55 Mean Change From Day 1 of Study 040 in Total SGRQ Score and Symptom, Activities and Impacts Scores for Subjects Randomised to Placebo in Studies 042 and 091

Week of Treatment	n	Assessment		Change from Day 1 of Study 040		
		Mean	Sd	Mean	sd	95% CI
Total Score						
Day 1a ²	212	36.4	18.0			
Week 24 ²	184	35.0	18.5	-1.9	12.3	-3.7, -0.1
Week 48 ²	170	35.6	17.4	-1.2	12.5	-3.1, 0.7
Week 72 ²	155	36.0	17.8	-0.6	13.7	-2.8, 1.6
Week 96 ²	142	34.2	18.3	-2.2	14.1	-4.5, 0.2
Week 120 ²	101	35.5	17.3	1.5	13.0	-1.1, 4.1
Endpoint ³	212	36.0	18.9	-0.4	14.0	-2.3, 1.5
Symptoms Score						
Day 1 ¹	213	41.9	23.1			
Week 24 ²	187	38.9	24.2	-4.3	22.2	-7.5, -1.1
Week 120 ²	105	39.1	21.8	-0.4	21.3	-4.6, 3.7
Endpoint ³	213	39.3	24.2	-2.7	23.0	-5.8, 0.4
Impacts Score						
Day 1 ¹	212	26.7	18.6			
Week 24 ²	184	25.0	18.9	-2.0	13.2	-4.0, -0.1
Week 120 ²	101	26.3	19.5	2.1	14.3	-0.7, 4.9
Endpoint ³	212	26.9	19.8	0.3	15.6	-1.9, 2.4
Activities Score						
Day 1 ¹	212	50.5	22.2			
Week 24 ²	184	50.2	22.7	-0.5	15.3	-2.7, 1.7
Week 120 ²	101	49.9	20.1	1.7	16.3	-1.5, 4.9
Endpoint ³	212	50.3	22.4	-0.2	16.1	-2.4, 2.0

Data Source: Section 14, [Table 14.7B](#), [Table 14.8B](#), [Table 14.9B](#), [Table 14.10B](#)

1. Day 1 is the baseline of study 040 and uses data from Week 24 of study 042 and Week 26 of study 091.
2. The week number is relative to the start of study 040.
3. Endpoint refers to last value reported on therapy.

In subjects randomised to placebo in studies 042 and 091, the mean change in total score from Day 1 of study 040 at study endpoint was -0.4. Results were similar for the symptoms, activities and impacts scores with only small changes from Day 1 being seen. Effects of treatment were greatest on the symptoms sub-score.

9.1.2. SF-36

The mean changes from baseline in the domain scores of the SF-36 are presented in Section 14, [Table 14.14A](#) to [Table 14.23A](#). The mean change from baseline in the physical composite score of the SF-36 for all subjects is presented graphically in Section 19, [Figure 19.14](#).

The mean change from baseline at endpoint for the composite scores and each of the domain scores is shown in [Table 56](#). For the SF-36, an increase in score indicates an improvement in health status.

Table 56 Mean Scores and Mean Change From Baseline¹ at Endpoint² in SF-36 Domain Scores for All Subjects

Prior Treatment	n	Endpoint ² Assessment		Change from Baseline ¹		
		Mean	sd	Mean	sd	95% CI
Physical composite Score³						
Prior Placebo	200	40.1	9.2	1.1	8.8	-0.1, 2.3
Prior SB-207499	410	41.3	9.7	0.9	8.6	0.0, 1.7
Mental composite Score⁴						
Prior Placebo	200	48.6	11.0	-2.3	10.8	-3.8, -0.8
Prior SB-207499	410	49.4	11.2	-1.7	10.4	-2.7, -0.7
Physical Functioning						
Prior Placebo	205	57.7	25.1	1.6	20.2	-1.2, 4.4
Prior SB-207499	437	57.8	26.5	1.3	21.3	-0.8, 3.3
Physical Role Functioning						
Prior Placebo	203	55.2	43.3	4.4	42.8	-1.5, 10.4
Prior SB-207499	423	61.9	42.3	3.2	43.8	-1.0, 7.4
Emotional Role Functioning						
Prior Placebo	204	66.0	41.8	-4.4	47.2	-10.9, 2.1
Prior SB-207499	429	69.2	42.2	-1.2	42.5	-5.2, 2.9
Social Functioning						
Prior Placebo	206	74.6	25.4	-5.0	24.5	-8.4, -1.7
Prior SB-207499	438	75.9	27.2	-5.2	23.3	-7.4, -3.0
Bodily Pain						
Prior Placebo	205	71.1	27.4	-1.6	27.2	-5.4, 2.1
Prior SB-207499	438	72.1	27.2	-1.3	26.8	-3.8, 1.3
Mental Health						
Prior Placebo	205	68.9	21.4	-2.7	18.3	-5.3, -0.2
Prior SB-207499	436	69.1	22.0	-3.5	19.5	-5.3, -1.7
Vitality						
Prior Placebo	205	53.7	22.0	-1.2	20.4	-4.0, 1.6
Prior SB-207499	436	53.9	23.8	-1.8	20.5	-3.7, 0.1
General Health Perceptions						
Prior Placebo	205	47.2	19.5	-0.0	18.3	-2.6, 2.5
Prior SB-207499	435	47.9	21.0	-1.1	18.9	-2.9, 0.7

Data Source: Section 14, [Table 14.14A](#), [Table 14.15A](#), [Table 14.16A](#), [Table 14.17A](#), [Table 14.18A](#), [Table 14.19A](#), [Table 14.20A](#), [Table 14.21A](#), [Table 14.22A](#), [Table 14.23A](#).

1. Baseline refers to the start of studies 042 and 091 and the week numbers are relative to baseline of these studies. Only subjects who continued in study 040 are included.
2. Endpoint refers to last value reported on therapy.
3. Summarises Physical Functioning and Physical Role Functioning scores
4. Summarises Emotional Role Functioning, Social Functioning, Mental Health and Vitality scores

In general, at endpoint, changes in SF-36 subscale scores were small and indicated a slight worsening of health status in most domains. Small improvements were seen in the physical composite score, the physical functioning score and the physical role functioning score.

9.2. Healthcare Utilisation

Healthcare utilisation data are presented in Section 18, [Table 18.1](#) to [Table 18.4](#) inclusive. A summary of healthcare utilisation is shown in [Table 57](#).

Table 57 Summary of COPD Related Healthcare Utilisation By Prior Treatment in Studies 042 and 091 – All Subjects

Prior Treatment	Exacerbation Level	Number of Subjects	Number of Utilisations
Placebo (n=243)	Physician Visit	115	406
	ER/Urgent Care	19	32
	Hospitalisation	21	29
	ICU Admission	2	2
	All Utilisations	117	450
SB-207499 (n =480)	Physician Visit	236	745
	ER/Urgent Care	47	70
	Hospitalisation	45	61
	ICU Admission	3	4
	All Utilisations	249	836

Data Source: Section 18, [Table 18.1](#)

The percentage of subjects having one or more utilisation was similar between the two prior treatment groups (prior placebo, 48.1%; prior SB-207499, 51.9%).

The healthcare utilisation rate per subject year of follow up was slightly higher for subjects in the prior placebo treatment group than those in the prior SB-207499 group. The rates were 0.955 (95% CI 0.871, 1.047) for the prior placebo treatment group and 0.834 (95% CI 0.779, 0.892) for the prior SB-207499 group (data source Section 18, [Table 18.2](#)).

Twenty-one subjects in the prior placebo group (11.6%) and 45 (9.4%) in the prior SB-207499 were hospitalised. The mean percentage of time in hospital (as a percentage of total time in the study for those who were hospitalised) was higher in the prior SB-207499 group (3.8%) than in the prior placebo group (1.8%) (Section 18, [Table 18.3](#)) but due to the lack of an adequate control group, no conclusions can be drawn regarding the effect of SB-207499 on the percentage of time spent in the hospital. Only 5 subjects, two in the prior placebo group and three in the prior SB-207499 group were admitted to the ICU during the study (Section 18, [Table 18.4](#)).

9.2.1. Days Lost from Work

Only 15 subjects, 5 in the prior placebo group and 10 in the prior SB-207499 group reported days lost from work (Section 18, [Table 18.5](#)). Subjects in the prior placebo

group had a mean of 1.177 days lost from work compared with a mean of 6.882 days lost from work for the prior SB-207499 group. Due to the low numbers of subjects reporting lost work days (which may be due to the collection method), no conclusions can be drawn regarding the effect of SB-207499 on the percentage of days lost from work. No information was collected on numbers of patients who actually work which may be limited due to the nature of the disease and the age of the population studied.

9.3. Health Outcomes Conclusions

At the start of study 040, subjects previously receiving placebo showed further decreases from baseline in SGRQ Total score but at endpoint both prior treatment groups had improvements of a similar size to those at the start of study 040. Similar effects were also seen on the symptoms, activities and impacts subscale scores. Some small effects were seen on some domains of the SF-36.

Healthcare utilisation was similar for the two prior treatment groups. The study design did not allow conclusions to be drawn as there was no adequate control group.

10. DISCUSSION

This was a multicentre, Phase III, open-label extension study in subjects with COPD. It was designed to evaluate the long-term safety of SB-207499 at a dose of 15mg twice daily. Efficacy assessments were also included but as all subjects included in the study received SB-207499 and had the option of using other medications for COPD, only limited conclusions on efficacy can be drawn. Prior to enrolment in this study, subjects had completed either study 042 or study 091 where subjects received SB-207499 15 mg twice daily or placebo for 24 weeks (042) or 26 weeks (091). This final report presents data collected up to 19 September 2002 when the study was terminated by the sponsor. GlaxoSmithKline, considered that that continuation of this protocol would not yield a better understanding of long-term drug safety and that alternative studies could be better used to improve our understanding of cilomilasts safety and efficacy. At the baseline of studies 042 and 091, the two treatment groups were well matched for demographic characteristics. Overall, the subjects represented a moderate COPD population (mean percentage predicted FEV₁ 50% of normal), although the study included a full spectrum of subjects ranging from mild to severe disease (range of FEV₁ 23% - 88% predicted). At screening, subjects had a mean FEV₁/FVC ratio of 0.55, low absolute reversibility to salbutamol (4.8%) and percent predicted TLCO of 69.7%. All subjects were current or ex-smokers. At entry, 43.4% were current smokers and the mean pack year smoking history was 44.4 pack years at screening. Few subjects changed smoking status during the study [128 (18%)]. The most common current medical condition in both groups (excluding COPD) was hypertension (24.6%). Incidence of chronic bronchitis was 10.4% and of emphysema was 8.0%, with similar incidences for these conditions in the two prior treatment groups.

Many subjects with COPD require treatment with a number of different COPD medications. On-demand inhaled beta₂-agonists and anticholinergic medication were permitted throughout the study and, where possible, stable doses were to be administered.

All other COPD medications with the exception of theophylline and aminophylline (oral and intravenous) were permitted without restriction during the study. Subjects were requested to refrain from using beta₂-agonists (short-acting) and anticholinergic medications during the 2-hour period preceding the visit and from using beta₂-agonists (long-acting) during the 12-hour period preceding the visit. If at all possible, the use of these medications was to be avoided during the clinic visits. Salbutamol and ipratropium bromide were the most commonly used concurrent medications in the study.

Compliance with study medication was good with 94.6% of subjects between 80 and 120% compliant during study treatment. The mean duration of exposure to study medication in this study was 744 days and 462 subjects (63.9%) had been in the study for longer than 2 years at the time of study termination. Subjects who had been treated with SB-207499 in studies 042 and 091 would have received an additional 24-26 weeks (168-182 days) of treatment with SB-207499.

Safety

The safety of SB-207499 was extensively assessed in this study with particular emphasis on cardiovascular and gastrointestinal monitoring. In addition to routine reporting of adverse experiences, the cardiovascular safety of SB-207499 was monitored by recording of sitting and orthostatic vital signs (Weeks 24 and 48, then every 48 weeks thereafter), and 12-lead ECGs at trough plasma levels (all visits).

In view of the known pharmacology of SB-207499, gastrointestinal adverse experiences were closely monitored; subjects were instructed to report within 24 hours any gastrointestinal symptoms which caused them concern or interfered with their daily activities (referred to as GIAEs of concern). Subjects were reminded to follow this procedure at each visit so reporting of these events was maximised and potentially enhanced by an increased placebo effect. Faecal occult blood testing and orthostatic vital signs assessments were performed in subjects experiencing GIAEs of concern (at the time of experience) and in all subjects every 48 weeks during the study and at their final study visit. Routine laboratory variables were also measured at regular intervals during the study.

This study has shown that SB-207499 taken long-term has a well-tolerated safety profile. Reflecting the long-term nature of the treatment period, almost all subjects reported at least one adverse experience during treatment; these were reported by 93.6% of subjects. The majority of on-therapy adverse experiences, those occurring in approximately 67% of subjects, were of mild or moderate intensity. Severe adverse experiences were experienced by 27.1% of subjects. The most common adverse experiences related to the respiratory, gastrointestinal, and body as a whole systems.

As expected in a study in this subject population and of this duration, the most frequently reported adverse experience was chronic obstructive airways disease (i.e. COPD exacerbation) which occurred in 68.3% of subjects. It is known that exacerbations are common in subjects with COPD [[Lams, 2000](#); [Murray, 1997](#); [National Institute of Health, 2001](#)]. The other most frequently reported adverse experiences were abdominal pain (16.3%), diarrhoea (14.1%) and injury (13.1%). Gastrointestinal adverse experiences (abdominal pain, diarrhoea, nausea, dyspepsia) and headache occurred at a

higher percentage in subjects who had previously taken placebo in studies 042 and 091 as these are increased mainly during the initial stages of treatment with SB-207499.

Adverse experiences that were considered to be, at least possibly study drug-related were reported by 196 subjects (27.1%), with abdominal pain, diarrhoea and nausea the most commonly reported potentially drug-related experiences. The gastrointestinal adverse experience profile was expected from the known pharmacology of the drug [Torphy, 1999] and the intensive monitoring for these adverse experiences.

A total of 123 subjects (17.0%) were withdrawn from this long-term study due to an adverse experience. The most frequent reasons which contributed to withdrawal were abdominal pain (24 subjects, 3.3%), COPD exacerbation (13 subjects, 1.8%), nausea and pulmonary carcinoma (each 11 subjects, 1.5%). Apart from pulmonary carcinoma, the incidences of these and most other adverse experiences contributing to subject withdrawal were greater in the group of subjects previously treated with placebo.

Abdominal pain caused the withdrawal of 13 subjects (5.3%) previously treated with placebo compared with 11 subjects (2.3%) previously treated with SB-207499. Of these 123 subjects, 47 were withdrawn due to adverse experiences that were considered by the Investigator to be drug-related.

Thirteen subjects died of events starting during the on-therapy study treatment period and 11 subjects died of events starting during the post-therapy period. None of the deaths was considered by the Investigator to be related to study medication. The cause of death in the majority of cases was related to the respiratory or cardiovascular system. This is consistent with this type of elderly subject population.

There were 203 subjects (28.1%) who experienced on-therapy serious adverse experiences. The most frequently occurring on-therapy serious adverse experiences were chronic obstructive airways disease (i.e. COPD exacerbation), occurring in 67 subjects (9.3%), pneumonia, occurring in 19 subjects (2.6%) and injury occurring in 17 subjects (2.4%). The serious adverse experience profile is also consistent for this subject population. Six subjects (four in the prior placebo treatment group and two in the prior SB-207499 treatment group) had serious adverse experiences that were considered by the Investigator to be possibly (suspected) related to study medication. Two subjects experienced GI haemorrhage, one subject experienced abdominal pain, diarrhoea and vomiting, one subject had abdominal pain, one subject experienced atrial fibrillation and one subject had a neoplasm (intestinal polyp).

During treatment with study medication, 97 subjects (13.4%) experienced 151 GIAEs of concern. This included 42 subjects (17.3%) and 55 subjects (11.5%) who had previously received placebo and SB-207499 respectively, in studies 042 and 091. Overall, the two most common GIAEs of concern were abdominal pain (6.1%) and diarrhoea (4.3%). With the exception of constipation, gastroenteritis, gastrointestinal disorder NOS, haemorrhoids and neoplasm NOS, all GIAEs of concern reported by more than one subject occurred in a higher percentage of subjects who previously received placebo. The majority (87%) of the 151 GIAEs of concern were mild or moderate in severity. One hundred and nine (59.6%) were considered to be related (suspected or probable) to study medication by the Investigator. Thirty-three subjects (4.6%), i.e. approximately one third of those with a GIAE of concern, were withdrawn because of their events. In general the

duration of these events was short and the majority resolved without sequelae and did not re-occur during continued treatment with SB-207499.

Routine faecal occult blood testing resulted in a positive result for 35 subjects (5.7%). This is in line with other cilomilast studies and no significant difference is seen between former placebo and former cilomilast populations. Faecal occult blood testing of subjects who experienced GIAEs of concern revealed a positive faecal occult blood test result in four patients. One further subject had a positive faecal occult blood test result at the safety follow-up visit after withdrawing for a GI haemorrhage.

In addition to these faecal occult blood tests, stool assessment at the time of a GIAE of concern showed that 11 subjects had blood in their stool; faecal occult blood tests at the time of the GIAE of concern were carried out on 6 of these subjects and two were positive. Of the 11 subjects, 5 reported melaena, three reported GI haemorrhage, one reported bloody diarrhoea, one reported haemorrhoids and one reported dyspepsia. Four subjects reported experiences that were suspected by the investigator to be study drug-related; three of these subjects reported black, tarry stools and one subject had normal stool with red blood on the outside (the reported adverse experience was dyspepsia). A majority of the 14 subjects with either a positive faecal occult blood test or blood in the stool at the time of a GIAE of concern continued treatment with SB-207499; only three subjects were withdrawn because of these events whilst one further subject withdrew due to nausea, diarrhoea and vomiting which coexisted with an adverse experience of melaena. All subjects who continued on therapy after suffering from a GIAE of concern plus blood (either trace or overt) did not experience any further gastrointestinal adverse events of concern or a repeat of a positive test for faecal occult blood at any subsequent visit. The mean time on therapy prior to study completion was post GIAE was 612.2 days without recurrence. Ten subjects who showed signs of blood in their stools in association with a GIAE of concern had further tests to explore the cause of this bleeding. Seven subjects had colonoscopies and four had upper digestive endoscopies/gastroscopy. Results of these investigations did not reveal any sinister pathology.

In summary, the intensive gastrointestinal monitoring performed in this study has not identified any new, serious, potentially drug related effects of long-term treatment with SB-207499 on the gastrointestinal tract. In addition, the results of this final analysis show no substantial differences to those of the interim report [[GSK Document Number SB-207499/RSD-1017MT/1](#)]. There was no evidence for a treatment effect of SB-207499 on faecal occult blood results or clinically important changes in orthostatic vital signs in subjects experiencing GIAEs of concern. Although some changes were seen during treatment, faecal occult blood testing and orthostatic vital signs assessments did not reveal any evidence for acute or chronic blood loss associated with long-term treatment with SB-207499. Only one subject who was assessed to have blood in their stool had haemoglobin values that were of potential clinical concern. This subject, who had black, tarry stools, was withdrawn from the study because of this event.

Overall, mean changes from baseline in haematological and clinical chemistry laboratory values were small, and the percentage of subjects with laboratory values of potential clinical concern was low. There was no evidence for an adverse effect of SB-207499 on laboratory parameters.

The percentages of subjects with transitions in sitting vital signs from normal at baseline to values of potential clinical concern on-therapy were low and there was no evidence for an adverse effect on vital signs following long-term treatment with SB-207499.

The most frequently occurring new-onset ECG abnormalities were an increase in QT interval (30.7%), premature ventricular contractions NOS (25.1%) and sinus bradycardia (23.0%). Mean QTc changes were low (0.3 msec in the former placebo group and 1.0 msec in the former SB-207499 group). These levels of change are similar to those seen for placebo and SB-207499 at endpoint in the feeder studies 042 and 091. Twelve-lead ECG abnormalities were reported as adverse experiences in 12.6% subjects. The majority of the adverse experiences were considered by the Investigator to be unrelated to study medication (i.e., not related or unlikely related). Overall, intensive 12-lead ECG monitoring did not raise any concerns about the cardiac safety of SB-207499.

Efficacy

The efficacy variables assessed in this study were pulmonary function tests (trough forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC), forced expiratory volume in 6 seconds (FEV₆), forced expiratory flow at 25-75% of vital capacity (FEF₂₅₋₇₅), forced expiratory flow at 75% of vital capacity (FEF₇₅) and peak expiratory flow rate (PEFR)), overall and post-exercise breathlessness, exercise performance (6-minute walk test) and COPD exacerbation rates. As there was no adequate control group in this study, effects of treatment on efficacy can only be assessed for variables where changes from baseline can be measured.

At the end of studies 042 and 091, the FEV₁ had decreased from baseline by a mean of 30 mL in the placebo group and increased from baseline by a mean of 10 mL in the SB-207499 group. Overall subjects showed a decrease in FEV₁ during study 040. At endpoint, the FEV₁ had decreased by a mean of 90 mL in the prior placebo group and 80 mL in the prior SB-207499 group as compared with baseline values of study 042 or study 091. Subjects switching from placebo to SB-207499 at the start of study 040 showed an initial increase in mean FEV₁ at the start of study 040, indicating a positive effect of treatment with SB-207499. FEV₁ declines with normal ageing at about 30 mL/year and this increases to around 70 mL/year in COPD subjects [Burrows, 1989]. Data from the placebo group in the ISOLDE study, a 3-year study, showed that the rate of decline in FEV₁ was 59 mL/year [Burge, 2000]. Therefore, a decline in FEV₁ would be expected over the course of this long term treatment period.. This may suggest the potential of a beneficial effect of SB-207499 on this measure, although further long-term placebo-controlled studies are needed to confirm this.

Results for other lung function parameters (FVC, PEFR, FEF₂₅₋₇₅, FEF₇₅, and FEV₆) were generally similar, with small decreases seen over the long term study period.

Improvements in breathlessness score were seen in the early part of the study in both treatment groups. At endpoint, the overall breathlessness score had decreased from baseline in the prior SB-207499 treatment group, indicating an improvement in breathlessness relative to baseline, but there was a increase in the prior placebo treatment

group. Results for the post-exercise dyspnoea scores were similar. Few differences from baseline in the distance walked in 6 minutes were seen.

COPD exacerbation rates per subject year of follow-up were 1.396 for the prior placebo group and 1.307 for the prior SB-207499 group. No conclusions can be drawn from these data due to lack of an adequate control group.

Health Outcomes

The health outcomes measures assessed in this study were total and subscale scores of the St George's Respiratory Questionnaire (SGRQ), subscales of the short form survey 36 (SF-36), and healthcare utilisation measures.

The SGRQ is a validated, disease-specific measure of health status [Jones, 1991]. A change of ≥ 4 units in the SGRQ total score has been shown to be of clinical relevance [Jones, 2002]. In this study, there were mean decreases from baseline in the total SGRQ score of 6.6 points in the prior placebo group and 6.2 points in the prior SB-207499 group, indicating a clinically relevant improvement relative to baseline. The symptoms, impacts and activities scores also decreased (i.e. improved) in both prior groups at study endpoint. Some small effects were also seen on some domains of the SF-36. For subjects in the prior placebo group, only very small changes from Day 1 of study 040 were seen in SGRQ at endpoint. As with FEV₁, these effects should be viewed in the context of the progressively deteriorating health status seen in subjects with COPD [Spencer, 2001]. However, with no adequate control group no conclusions can be made about a reduction in this rate of decline.

Healthcare utilisation was similar for the two prior treatment groups. Very few subjects reported any days lost from work during the study although this largely reflects the health status and demography of the study population.

11. CONCLUSIONS

Long-term treatment with SB-207499 15 mg twice daily was well tolerated with no new or serious safety issues identified. After a further 6 months of the study, results showed no substantial differences to those of the interim analysis in March 2002. There was no evidence for any adverse effects of long-term drug administration on vital signs, ECG or laboratory variables. Intensive GI monitoring has not revealed any long term safety concerns.

A small decline in FEV₁ was seen although this was smaller than might have been expected over this long-term treatment period. Improvements in health status were maintained over the study.

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* **ARIFLO** is a Trademark of the GlaxoSmithKline group of companies.

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13. STUDY POPULATION DATA SOURCE TABLES

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TABLE 13.1A

SUMMARY OF PATIENT DISPOSITION BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PRIOR TREATMENT

DISPOSITION	PLACEBO (N=243)	SB 207499 (N=480)	TOTAL (N=723)

ENROLLED	243 (100.0%)	480 (100.0%)	723 (100.0%)
EFFICACY ANALYSIS	232 (95.5%)	469 (97.7%)	701 (97.0%)
SAFETY ANALYSIS	243 (100.0%)	480 (100.0%)	723 (100.0%)

1. SAMPLE SIZE REFLECTS THE PERCENTAGE OF PATIENTS ENROLLED

2. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 13.1B

SUMMARY OF PATIENT DISPOSITION BY COUNTRY, CENTER AND BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

COUNTRY	CENTER	DISPOSITION	PRIOR TREATMENT		TOTAL (N=723)
			PLACEBO (N=243)	SB 207499 (N=480)	
AUSTRALIA		ENROLLED	0	1 (100.0%)	1 (100.0%)
		EFFICACY	0	1 (100.0%)	1 (100.0%)
		ENROLLED	1 (100.0%)	2 (100.0%)	3 (100.0%)
		EFFICACY	1 (100.0%)	2 (100.0%)	3 (100.0%)
		ENROLLED	1 (100.0%)	4 (100.0%)	5 (100.0%)
		EFFICACY	1 (100.0%)	4 (100.0%)	5 (100.0%)
		ENROLLED	3 (100.0%)	4 (100.0%)	7 (100.0%)
		EFFICACY	2 (66.7%)	4 (100.0%)	6 (85.7%)
		ENROLLED	1 (100.0%)	2 (100.0%)	3 (100.0%)
		EFFICACY	1 (100.0%)	2 (100.0%)	3 (100.0%)
BELGIUM	TOTAL	ENROLLED	6 (100.0%)	13 (100.0%)	19 (100.0%)
		EFFICACY	5 (83.3%)	13 (100.0%)	18 (94.7%)
		ENROLLED	4 (100.0%)	9 (100.0%)	13 (100.0%)
		EFFICACY	4 (100.0%)	9 (100.0%)	13 (100.0%)
		ENROLLED	2 (100.0%)	2 (100.0%)	4 (100.0%)
		EFFICACY	2 (100.0%)	2 (100.0%)	4 (100.0%)
		ENROLLED	2 (100.0%)	2 (100.0%)	4 (100.0%)
		EFFICACY	2 (100.0%)	2 (100.0%)	4 (100.0%)
		ENROLLED	1 (100.0%)	0	1 (100.0%)
		EFFICACY	1 (100.0%)	0	1 (100.0%)
FINLAND	TOTAL	ENROLLED	9 (100.0%)	13 (100.0%)	22 (100.0%)
		EFFICACY	9 (100.0%)	13 (100.0%)	22 (100.0%)
		ENROLLED	4 (100.0%)	3 (100.0%)	7 (100.0%)
		EFFICACY	4 (100.0%)	3 (100.0%)	7 (100.0%)
		ENROLLED	3 (100.0%)	4 (100.0%)	7 (100.0%)
		EFFICACY	3 (100.0%)	4 (100.0%)	7 (100.0%)
		ENROLLED	1 (100.0%)	5 (100.0%)	6 (100.0%)
		EFFICACY	1 (100.0%)	5 (100.0%)	6 (100.0%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED WITHIN EACH CENTER/COUNTRY
2. TOTAL ROWS REPRESENT THE TOTAL FOR ALL OF THE CENTERS WITHIN A COUNTRY
3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042/091

TABLE 13.1B

SUMMARY OF PATIENT DISPOSITION BY COUNTRY, CENTER AND BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

COUNTRY	CENTER	DISPOSITION	PRIOR TREATMENT		TOTAL (N=723)
			PLACEBO (N=243)	SB 207499 (N=480)	
FINLAND		ENROLLED	2 (100.0%)	5 (100.0%)	7 (100.0%)
		EFFICACY	2 (100.0%)	5 (100.0%)	7 (100.0%)
		ENROLLED	3 (100.0%)	4 (100.0%)	7 (100.0%)
		EFFICACY	2 (66.7%)	4 (100.0%)	6 (85.7%)
		ENROLLED	3 (100.0%)	8 (100.0%)	11 (100.0%)
		EFFICACY	3 (100.0%)	7 (87.5%)	10 (90.9%)
	TOTAL	ENROLLED	16 (100.0%)	29 (100.0%)	45 (100.0%)
		EFFICACY	15 (93.8%)	28 (96.6%)	43 (95.6%)
FRANCE		ENROLLED	1 (100.0%)	0 .	1 (100.0%)
		EFFICACY	1 (100.0%)	0 .	1 (100.0%)
		ENROLLED	8 (100.0%)	15 (100.0%)	23 (100.0%)
		EFFICACY	8 (100.0%)	15 (100.0%)	23 (100.0%)
		ENROLLED	1 (100.0%)	0 .	1 (100.0%)
		EFFICACY	1 (100.0%)	0 .	1 (100.0%)
		ENROLLED	2 (100.0%)	9 (100.0%)	11 (100.0%)
		EFFICACY	2 (100.0%)	8 (88.9%)	10 (90.9%)
		ENROLLED	8 (100.0%)	13 (100.0%)	21 (100.0%)
		EFFICACY	8 (100.0%)	13 (100.0%)	21 (100.0%)
		ENROLLED	1 (100.0%)	3 (100.0%)	4 (100.0%)
		EFFICACY	1 (100.0%)	3 (100.0%)	4 (100.0%)
		ENROLLED	0 .	3 (100.0%)	3 (100.0%)
		EFFICACY	0 .	3 (100.0%)	3 (100.0%)
		ENROLLED	2 (100.0%)	4 (100.0%)	6 (100.0%)
		EFFICACY	2 (100.0%)	4 (100.0%)	6 (100.0%)
		ENROLLED	1 (100.0%)	0 .	1 (100.0%)
		EFFICACY	1 (100.0%)	0 .	1 (100.0%)
		ENROLLED	2 (100.0%)	4 (100.0%)	6 (100.0%)
		EFFICACY	2 (100.0%)	4 (100.0%)	6 (100.0%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED WITHIN EACH CENTER/COUNTRY
2. TOTAL ROWS REPRESENT THE TOTAL FOR ALL OF THE CENTERS WITHIN A COUNTRY
3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042/091

TABLE 13.1B

SUMMARY OF PATIENT DISPOSITION BY COUNTRY, CENTER AND BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

COUNTRY	CENTER	DISPOSITION	PRIOR TREATMENT		TOTAL (N=723)
			PLACEBO (N=243)	SB 207499 (N=480)	
FRANCE		ENROLLED	2 (100.0%)	6 (100.0%)	8 (100.0%)
		EFFICACY	2 (100.0%)	6 (100.0%)	8 (100.0%)
		ENROLLED	1 (100.0%)	3 (100.0%)	4 (100.0%)
		EFFICACY	1 (100.0%)	3 (100.0%)	4 (100.0%)
		ENROLLED	1 (100.0%)	1 (100.0%)	2 (100.0%)
		EFFICACY	1 (100.0%)	1 (100.0%)	2 (100.0%)
		ENROLLED	1 (100.0%)	1 (100.0%)	2 (100.0%)
		EFFICACY	1 (100.0%)	1 (100.0%)	2 (100.0%)
		ENROLLED	1 (100.0%)	1 (100.0%)	2 (100.0%)
		EFFICACY	1 (100.0%)	1 (100.0%)	2 (100.0%)
		ENROLLED	0 .	1 (100.0%)	1 (100.0%)
		EFFICACY	0 .	1 (100.0%)	1 (100.0%)
		ENROLLED	9 (100.0%)	18 (100.0%)	27 (100.0%)
		EFFICACY	9 (100.0%)	18 (100.0%)	27 (100.0%)
GERMANY		ENROLLED	0 .	1 (100.0%)	1 (100.0%)
		EFFICACY	0 .	1 (100.0%)	1 (100.0%)
		ENROLLED	0 .	3 (100.0%)	3 (100.0%)
		EFFICACY	0 .	3 (100.0%)	3 (100.0%)
		ENROLLED	3 (100.0%)	4 (100.0%)	7 (100.0%)
		EFFICACY	3 (100.0%)	4 (100.0%)	7 (100.0%)
		TOTAL	44 (100.0%)	90 (100.0%)	134 (100.0%)
		ENROLLED	44 (100.0%)	89 (98.9%)	133 (99.3%)
		ENROLLED	0 .	1 (100.0%)	1 (100.0%)
		EFFICACY	0 .	1 (100.0%)	1 (100.0%)
		ENROLLED	1 (100.0%)	1 (100.0%)	2 (100.0%)
		EFFICACY	1 (100.0%)	1 (100.0%)	2 (100.0%)
		ENROLLED	1 (100.0%)	1 (100.0%)	2 (100.0%)
		EFFICACY	1 (100.0%)	1 (100.0%)	2 (100.0%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED WITHIN EACH CENTER/COUNTRY
2. TOTAL ROWS REPRESENT THE TOTAL FOR ALL OF THE CENTERS WITHIN A COUNTRY
3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042/091

TABLE 13.1B

SUMMARY OF PATIENT DISPOSITION BY COUNTRY, CENTER AND BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

COUNTRY	CENTER	DISPOSITION	PRIOR TREATMENT		TOTAL (N=723)
			PLACEBO (N=243)	SB 207499 (N=480)	
GERMANY		ENROLLED	2 (100.0%)	6 (100.0%)	8 (100.0%)
		EFFICACY	2 (100.0%)	6 (100.0%)	8 (100.0%)
		ENROLLED	3 (100.0%)	7 (100.0%)	10 (100.0%)
		EFFICACY	3 (100.0%)	7 (100.0%)	10 (100.0%)
		ENROLLED	1 (100.0%)	3 (100.0%)	4 (100.0%)
		EFFICACY	1 (100.0%)	3 (100.0%)	4 (100.0%)
		ENROLLED	1 (100.0%)	3 (100.0%)	4 (100.0%)
		EFFICACY	1 (100.0%)	3 (100.0%)	4 (100.0%)
		ENROLLED	0 .	1 (100.0%)	1 (100.0%)
		EFFICACY	0 .	1 (100.0%)	1 (100.0%)
		ENROLLED	3 (100.0%)	15 (100.0%)	18 (100.0%)
		EFFICACY	3 (100.0%)	15 (100.0%)	18 (100.0%)
		ENROLLED	0 .	1 (100.0%)	1 (100.0%)
		EFFICACY	0 .	1 (100.0%)	1 (100.0%)
		ENROLLED	0 .	1 (100.0%)	1 (100.0%)
		EFFICACY	0 .	1 (100.0%)	1 (100.0%)
		ENROLLED	0 .	1 (100.0%)	1 (100.0%)
		EFFICACY	0 .	0 .	0 .
		ENROLLED	0 .	1 (100.0%)	1 (100.0%)
		EFFICACY	0 .	1 (100.0%)	1 (100.0%)
		ENROLLED	5 (100.0%)	7 (100.0%)	12 (100.0%)
		EFFICACY	2 (40.0%)	6 (85.7%)	8 (66.7%)
		ENROLLED	1 (100.0%)	3 (100.0%)	4 (100.0%)
		EFFICACY	1 (100.0%)	2 (66.7%)	3 (75.0%)
		ENROLLED	2 (100.0%)	3 (100.0%)	5 (100.0%)
		EFFICACY	2 (100.0%)	3 (100.0%)	5 (100.0%)
		ENROLLED	11 (100.0%)	22 (100.0%)	33 (100.0%)
		EFFICACY	10 (90.9%)	21 (95.5%)	31 (93.9%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED WITHIN EACH CENTER/COUNTRY

2. TOTAL ROWS REPRESENT THE TOTAL FOR ALL OF THE CENTERS WITHIN A COUNTRY

3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042/091

TABLE 13.1B

SUMMARY OF PATIENT DISPOSITION BY COUNTRY, CENTER AND BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

COUNTRY	CENTER	DISPOSITION	PRIOR TREATMENT		TOTAL (N=723)
			PLACEBO (N=243)	SB 207499 (N=480)	
GERMANY		ENROLLED	1 (100.0%)	2 (100.0%)	3 (100.0%)
		EFFICACY	1 (100.0%)	2 (100.0%)	3 (100.0%)
		ENROLLED	1 (100.0%)	1 (100.0%)	2 (100.0%)
		EFFICACY	1 (100.0%)	1 (100.0%)	2 (100.0%)
		ENROLLED	0 .	1 (100.0%)	1 (100.0%)
		EFFICACY	0 .	1 (100.0%)	1 (100.0%)
		ENROLLED	0 .	1 (100.0%)	1 (100.0%)
		EFFICACY	0 .	1 (100.0%)	1 (100.0%)
		ENROLLED	2 (100.0%)	8 (100.0%)	10 (100.0%)
		EFFICACY	2 (100.0%)	6 (75.0%)	8 (80.0%)
		ENROLLED	1 (100.0%)	3 (100.0%)	4 (100.0%)
		EFFICACY	1 (100.0%)	3 (100.0%)	4 (100.0%)
		ENROLLED	1 (100.0%)	2 (100.0%)	3 (100.0%)
		EFFICACY	1 (100.0%)	2 (100.0%)	3 (100.0%)
		ENROLLED	0 .	1 (100.0%)	1 (100.0%)
		EFFICACY	0 .	1 (100.0%)	1 (100.0%)
		ENROLLED	1 (100.0%)	1 (100.0%)	2 (100.0%)
		EFFICACY	1 (100.0%)	1 (100.0%)	2 (100.0%)
	TOTAL	ENROLLED	38 (100.0%)	97 (100.0%)	135 (100.0%)
		EFFICACY	34 (89.5%)	91 (93.8%)	125 (92.6%)
NETHERLANDS		ENROLLED	2 (100.0%)	2 (100.0%)	4 (100.0%)
		EFFICACY	2 (100.0%)	2 (100.0%)	4 (100.0%)
		ENROLLED	1 (100.0%)	1 (100.0%)	2 (100.0%)
		EFFICACY	1 (100.0%)	1 (100.0%)	2 (100.0%)
		ENROLLED	1 (100.0%)	4 (100.0%)	5 (100.0%)
		EFFICACY	0 .	4 (100.0%)	4 (80.0%)
	TOTAL	ENROLLED	4 (100.0%)	7 (100.0%)	11 (100.0%)
		EFFICACY	3 (75.0%)	7 (100.0%)	10 (90.9%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED WITHIN EACH CENTER/COUNTRY
2. TOTAL ROWS REPRESENT THE TOTAL FOR ALL OF THE CENTERS WITHIN A COUNTRY
3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042/091

TABLE 13.1B

SUMMARY OF PATIENT DISPOSITION BY COUNTRY, CENTER AND BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

COUNTRY	CENTER	DISPOSITION	PRIOR TREATMENT		TOTAL (N=723)
			PLACEBO (N=243)	SB 207499 (N=480)	
NORWAY		ENROLLED	2 (100.0%)	1 (100.0%)	3 (100.0%)
		EFFICACY	2 (100.0%)	1 (100.0%)	3 (100.0%)
		ENROLLED	3 (100.0%)	4 (100.0%)	7 (100.0%)
		EFFICACY	3 (100.0%)	4 (100.0%)	7 (100.0%)
		ENROLLED	1 (100.0%)	6 (100.0%)	7 (100.0%)
		EFFICACY	1 (100.0%)	6 (100.0%)	7 (100.0%)
		ENROLLED	0 .	1 (100.0%)	1 (100.0%)
		EFFICACY	0 .	1 (100.0%)	1 (100.0%)
		ENROLLED	1 (100.0%)	1 (100.0%)	2 (100.0%)
		EFFICACY	1 (100.0%)	1 (100.0%)	2 (100.0%)
		ENROLLED	1 (100.0%)	2 (100.0%)	3 (100.0%)
		EFFICACY	1 (100.0%)	2 (100.0%)	3 (100.0%)
		ENROLLED	1 (100.0%)	1 (100.0%)	2 (100.0%)
		EFFICACY	1 (100.0%)	1 (100.0%)	2 (100.0%)
	TOTAL	ENROLLED	10 (100.0%)	17 (100.0%)	27 (100.0%)
		EFFICACY	10 (100.0%)	17 (100.0%)	27 (100.0%)
PORTUGAL		ENROLLED	0 .	1 (100.0%)	1 (100.0%)
		EFFICACY	0 .	1 (100.0%)	1 (100.0%)
	TOTAL	ENROLLED	0 .	1 (100.0%)	1 (100.0%)
		EFFICACY	0 .	1 (100.0%)	1 (100.0%)
SOUTH AFRICA		ENROLLED	1 (100.0%)	4 (100.0%)	5 (100.0%)
		EFFICACY	1 (100.0%)	4 (100.0%)	5 (100.0%)
		ENROLLED	2 (100.0%)	1 (100.0%)	3 (100.0%)
		EFFICACY	2 (100.0%)	1 (100.0%)	3 (100.0%)
		ENROLLED	1 (100.0%)	0 .	1 (100.0%)
		EFFICACY	1 (100.0%)	0 .	1 (100.0%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED WITHIN EACH CENTER/COUNTRY

2. TOTAL ROWS REPRESENT THE TOTAL FOR ALL OF THE CENTERS WITHIN A COUNTRY

3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042/091

TABLE 13.1B

SUMMARY OF PATIENT DISPOSITION BY COUNTRY, CENTER AND BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

COUNTRY	CENTER	DISPOSITION	PRIOR TREATMENT		TOTAL (N=723)
			PLACEBO (N=243)	SB 207499 (N=480)	
SOUTH AFRICA		ENROLLED	0	1 (100.0%)	1 (100.0%)
		EFFICACY	0	1 (100.0%)	1 (100.0%)
		ENROLLED	0	1 (100.0%)	1 (100.0%)
		EFFICACY	0	1 (100.0%)	1 (100.0%)
		ENROLLED	1 (100.0%)	3 (100.0%)	4 (100.0%)
		EFFICACY	1 (100.0%)	3 (100.0%)	4 (100.0%)
		ENROLLED	0	2 (100.0%)	2 (100.0%)
		EFFICACY	0	2 (100.0%)	2 (100.0%)
		TOTAL	5 (100.0%)	12 (100.0%)	17 (100.0%)
		EFFICACY	5 (100.0%)	12 (100.0%)	17 (100.0%)
SPAIN		ENROLLED	2 (100.0%)	0	2 (100.0%)
		EFFICACY	2 (100.0%)	0	2 (100.0%)
		ENROLLED	1 (100.0%)	6 (100.0%)	7 (100.0%)
		EFFICACY	1 (100.0%)	6 (100.0%)	7 (100.0%)
		ENROLLED	0	2 (100.0%)	2 (100.0%)
		EFFICACY	0	2 (100.0%)	2 (100.0%)
		ENROLLED	0	3 (100.0%)	3 (100.0%)
		EFFICACY	0	3 (100.0%)	3 (100.0%)
		ENROLLED	0	1 (100.0%)	1 (100.0%)
		EFFICACY	0	1 (100.0%)	1 (100.0%)
		ENROLLED	2 (100.0%)	4 (100.0%)	6 (100.0%)
		EFFICACY	2 (100.0%)	4 (100.0%)	6 (100.0%)
		ENROLLED	5 (100.0%)	7 (100.0%)	12 (100.0%)
		EFFICACY	5 (100.0%)	7 (100.0%)	12 (100.0%)
		ENROLLED	1 (100.0%)	4 (100.0%)	5 (100.0%)
		EFFICACY	1 (100.0%)	4 (100.0%)	5 (100.0%)
		ENROLLED	1 (100.0%)	4 (100.0%)	5 (100.0%)
		EFFICACY	1 (100.0%)	4 (100.0%)	5 (100.0%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED WITHIN EACH CENTER/COUNTRY
2. TOTAL ROWS REPRESENT THE TOTAL FOR ALL OF THE CENTERS WITHIN A COUNTRY
3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042/091

TABLE 13.1B

SUMMARY OF PATIENT DISPOSITION BY COUNTRY, CENTER AND BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

COUNTRY	CENTER	DISPOSITION	PRIOR TREATMENT		TOTAL (N=723)
			PLACEBO (N=243)	SB 207499 (N=480)	
SPAIN		ENROLLED	4 (100.0%)	4 (100.0%)	8 (100.0%)
		EFFICACY	4 (100.0%)	4 (100.0%)	8 (100.0%)
		ENROLLED	0 .	2 (100.0%)	2 (100.0%)
		EFFICACY	0 .	2 (100.0%)	2 (100.0%)
		ENROLLED	1 (100.0%)	5 (100.0%)	6 (100.0%)
		EFFICACY	1 (100.0%)	5 (100.0%)	6 (100.0%)
		ENROLLED	3 (100.0%)	8 (100.0%)	11 (100.0%)
		EFFICACY	3 (100.0%)	8 (100.0%)	11 (100.0%)
		ENROLLED	2 (100.0%)	1 (100.0%)	3 (100.0%)
		EFFICACY	2 (100.0%)	1 (100.0%)	3 (100.0%)
		ENROLLED	3 (100.0%)	6 (100.0%)	9 (100.0%)
		EFFICACY	2 (66.7%)	6 (100.0%)	8 (88.9%)
		ENROLLED	1 (100.0%)	1 (100.0%)	2 (100.0%)
		EFFICACY	1 (100.0%)	1 (100.0%)	2 (100.0%)
		ENROLLED	4 (100.0%)	10 (100.0%)	14 (100.0%)
		EFFICACY	4 (100.0%)	10 (100.0%)	14 (100.0%)
		ENROLLED	1 (100.0%)	1 (100.0%)	2 (100.0%)
		EFFICACY	1 (100.0%)	1 (100.0%)	2 (100.0%)
		ENROLLED	1 (100.0%)	2 (100.0%)	3 (100.0%)
		EFFICACY	1 (100.0%)	2 (100.0%)	3 (100.0%)
		ENROLLED	2 (100.0%)	3 (100.0%)	5 (100.0%)
		EFFICACY	2 (100.0%)	3 (100.0%)	5 (100.0%)
		ENROLLED	4 (100.0%)	5 (100.0%)	9 (100.0%)
		EFFICACY	4 (100.0%)	5 (100.0%)	9 (100.0%)
		ENROLLED	3 (100.0%)	7 (100.0%)	10 (100.0%)
		EFFICACY	3 (100.0%)	7 (100.0%)	10 (100.0%)
		ENROLLED	2 (100.0%)	3 (100.0%)	5 (100.0%)
		EFFICACY	2 (100.0%)	2 (66.7%)	4 (80.0%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED WITHIN EACH CENTER/COUNTRY
2. TOTAL ROWS REPRESENT THE TOTAL FOR ALL OF THE CENTERS WITHIN A COUNTRY
3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042/091

TABLE 13.1B

SUMMARY OF PATIENT DISPOSITION BY COUNTRY, CENTER AND BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

COUNTRY	CENTER	DISPOSITION	PRIOR TREATMENT		TOTAL	
			PLACEBO (N=243)	SB 207499 (N=480)	(N=723)	
SPAIN		ENROLLED	4 (100.0%)	6 (100.0%)	10 (100.0%)	
		EFFICACY	4 (100.0%)	6 (100.0%)	10 (100.0%)	
		ENROLLED	4 (100.0%)	5 (100.0%)	9 (100.0%)	
		EFFICACY	4 (100.0%)	5 (100.0%)	9 (100.0%)	
		ENROLLED	3 (100.0%)	6 (100.0%)	9 (100.0%)	
		EFFICACY	3 (100.0%)	6 (100.0%)	9 (100.0%)	
		ENROLLED	5 (100.0%)	8 (100.0%)	13 (100.0%)	
		EFFICACY	5 (100.0%)	8 (100.0%)	13 (100.0%)	
		ENROLLED	4 (100.0%)	4 (100.0%)	8 (100.0%)	
		EFFICACY	4 (100.0%)	3 (75.0%)	7 (87.5%)	
		ENROLLED	3 (100.0%)	7 (100.0%)	10 (100.0%)	
		EFFICACY	2 (66.7%)	7 (100.0%)	9 (90.0%)	
		ENROLLED	2 (100.0%)	2 (100.0%)	4 (100.0%)	
		EFFICACY	2 (100.0%)	2 (100.0%)	4 (100.0%)	
		ENROLLED	1 (100.0%)	3 (100.0%)	4 (100.0%)	
		EFFICACY	1 (100.0%)	3 (100.0%)	4 (100.0%)	
		ENROLLED	3 (100.0%)	3 (100.0%)	6 (100.0%)	
		EFFICACY	3 (100.0%)	3 (100.0%)	6 (100.0%)	
		ENROLLED	0 .	3 (100.0%)	3 (100.0%)	
		EFFICACY	0 .	3 (100.0%)	3 (100.0%)	
		ENROLLED	1 (100.0%)	3 (100.0%)	4 (100.0%)	
		EFFICACY	1 (100.0%)	3 (100.0%)	4 (100.0%)	
		ENROLLED	0 .	1 (100.0%)	1 (100.0%)	
		EFFICACY	0 .	1 (100.0%)	1 (100.0%)	
		ENROLLED	1 (100.0%)	3 (100.0%)	4 (100.0%)	
		EFFICACY	0 .	3 (100.0%)	3 (75.0%)	
		ENROLLED	3 (100.0%)	2 (100.0%)	5 (100.0%)	
		EFFICACY	3 (100.0%)	2 (100.0%)	5 (100.0%)	

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED WITHIN EACH CENTER/COUNTRY
2. TOTAL ROWS REPRESENT THE TOTAL FOR ALL OF THE CENTERS WITHIN A COUNTRY
3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042/091

TABLE 13.1B

SUMMARY OF PATIENT DISPOSITION BY COUNTRY, CENTER AND BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

COUNTRY	CENTER	DISPOSITION	PRIOR TREATMENT		TOTAL (N=723)
			PLACEBO (N=243)	SB 207499 (N=480)	
SPAIN		ENROLLED	1 (100.0%)	3 (100.0%)	4 (100.0%)
		EFFICACY	1 (100.0%)	3 (100.0%)	4 (100.0%)
		ENROLLED	1 (100.0%)	5 (100.0%)	6 (100.0%)
		EFFICACY	1 (100.0%)	5 (100.0%)	6 (100.0%)
		ENROLLED	0 .	1 (100.0%)	1 (100.0%)
		EFFICACY	0 .	1 (100.0%)	1 (100.0%)
		ENROLLED	1 (100.0%)	1 (100.0%)	2 (100.0%)
		EFFICACY	1 (100.0%)	1 (100.0%)	2 (100.0%)
		TOTAL	80 (100.0%)	155 (100.0%)	235 (100.0%)
		EFFICACY	77 (96.3%)	153 (98.7%)	230 (97.9%)
UNITED KINGDOM		ENROLLED	11 (100.0%)	14 (100.0%)	25 (100.0%)
		EFFICACY	11 (100.0%)	14 (100.0%)	25 (100.0%)
		ENROLLED	1 (100.0%)	2 (100.0%)	3 (100.0%)
		EFFICACY	1 (100.0%)	2 (100.0%)	3 (100.0%)
		ENROLLED	1 (100.0%)	2 (100.0%)	3 (100.0%)
		EFFICACY	1 (100.0%)	2 (100.0%)	3 (100.0%)
		ENROLLED	1 (100.0%)	1 (100.0%)	2 (100.0%)
		EFFICACY	1 (100.0%)	1 (100.0%)	2 (100.0%)
		ENROLLED	1 (100.0%)	5 (100.0%)	6 (100.0%)
		EFFICACY	0 .	5 (100.0%)	5 (83.3%)
		ENROLLED	2 (100.0%)	4 (100.0%)	6 (100.0%)
		EFFICACY	2 (100.0%)	3 (75.0%)	5 (83.3%)
		ENROLLED	5 (100.0%)	5 (100.0%)	10 (100.0%)
		EFFICACY	5 (100.0%)	5 (100.0%)	10 (100.0%)
		ENROLLED	1 (100.0%)	0 .	1 (100.0%)
		EFFICACY	1 (100.0%)	0 .	1 (100.0%)
		ENROLLED	6 (100.0%)	6 (100.0%)	12 (100.0%)
		EFFICACY	6 (100.0%)	6 (100.0%)	12 (100.0%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED WITHIN EACH CENTER/COUNTRY
2. TOTAL ROWS REPRESENT THE TOTAL FOR ALL OF THE CENTERS WITHIN A COUNTRY
3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042/091

TABLE 13.1B

SUMMARY OF PATIENT DISPOSITION BY COUNTRY, CENTER AND BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

COUNTRY	CENTER	DISPOSITION	PRIOR TREATMENT		TOTAL (N=723)
			PLACEBO (N=243)	SB 207499 (N=480)	
UNITED KINGDOM		ENROLLED	2 (100.0%)	7 (100.0%)	9 (100.0%)
		EFFICACY	2 (100.0%)	7 (100.0%)	9 (100.0%)
	TOTAL	ENROLLED	31 (100.0%)	46 (100.0%)	77 (100.0%)
		EFFICACY	30 (96.8%)	45 (97.8%)	75 (97.4%)
TOTAL	TOTAL	ENROLLED	243 (100.0%)	480 (100.0%)	723 (100.0%)
		EFFICACY	232 (95.5%)	469 (97.7%)	701 (97.0%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED WITHIN EACH CENTER/COUNTRY
2. TOTAL ROWS REPRESENT THE TOTAL FOR ALL OF THE CENTERS WITHIN A COUNTRY
3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042/091

TABLE 13.2

DISTRIBUTION OF PATIENTS IN STUDY BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

VISIT/WEEK	PRIOR TREATMENT				TOTAL	
	PLACEBO (N=243)		SB 207499 (N=480)		(N=723)	
VISIT 1/DAY 1	243	(100.0%)	480	(100.0%)	723	(100.0%)
VISIT 2/WEEK 1	241	(99.2%)	474	(98.8%)	715	(98.9%)
VISIT 3/WEEK 2	233	(95.9%)	461	(96.0%)	694	(96.0%)
VISIT 4/WEEK 4	222	(91.4%)	461	(96.0%)	683	(94.5%)
VISIT 5/WEEK 8	214	(88.1%)	453	(94.4%)	667	(92.3%)
VISIT 6/WEEK 12	211	(86.8%)	446	(92.9%)	657	(90.9%)
VISIT 7/WEEK 16	202	(83.1%)	438	(91.3%)	640	(88.5%)
VISIT 8/WEEK 20	198	(81.5%)	437	(91.0%)	635	(87.8%)
VISIT 9/WEEK 24	194	(79.8%)	429	(89.4%)	623	(86.2%)
VISIT 10/WEEK 28	191	(78.6%)	423	(88.1%)	614	(84.9%)
VISIT 11/WEEK 32	188	(77.4%)	419	(87.3%)	607	(84.0%)
VISIT 12/WEEK 36	187	(77.0%)	414	(86.3%)	601	(83.1%)
VISIT 13/WEEK 40	186	(76.5%)	408	(85.0%)	594	(82.2%)
VISIT 14/WEEK 44	184	(75.7%)	406	(84.6%)	590	(81.6%)
VISIT 15/WEEK 48	184	(75.7%)	403	(84.0%)	587	(81.2%)
VISIT 16/WEEK 52	180	(74.1%)	388	(80.8%)	568	(78.6%)
VISIT 17/WEEK 56	173	(71.2%)	367	(76.5%)	540	(74.7%)
VISIT 18/WEEK 60	174	(71.6%)	376	(78.3%)	550	(76.1%)
VISIT 19/WEEK 64	142	(58.4%)	311	(64.8%)	453	(62.7%)
VISIT 20/WEEK 68	140	(57.6%)	300	(62.5%)	440	(60.9%)
VISIT 21/WEEK 72	172	(70.8%)	359	(74.8%)	531	(73.4%)
VISIT 22/WEEK 76	100	(41.2%)	199	(41.5%)	299	(41.4%)

1. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 13.2

DISTRIBUTION OF PATIENTS IN STUDY BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

VISIT/WEEK	PRIOR TREATMENT				TOTAL	
	PLACEBO (N=243)		SB 207499 (N=480)		(N=723)	
VISIT 23/WEEK 80	99	(40.7%)	194	(40.4%)	293	(40.5%)
VISIT 24/WEEK 84	163	(67.1%)	337	(70.2%)	500	(69.2%)
VISIT 25/WEEK 88	53	(21.8%)	97	(20.2%)	150	(20.7%)
VISIT 26/WEEK 92	52	(21.4%)	96	(20.0%)	148	(20.5%)
VISIT 27/WEEK 96	160	(65.8%)	333	(69.4%)	493	(68.2%)
VISIT 28/WEEK 100	22	(9.1%)	50	(10.4%)	72	(10.0%)
VISIT 29/WEEK 104	18	(7.4%)	40	(8.3%)	58	(8.0%)
VISIT 30/WEEK 108	130	(53.5%)	278	(57.9%)	408	(56.4%)
VISIT 31/WEEK 112	9	(3.7%)	18	(3.8%)	27	(3.7%)
VISIT 32/WEEK 116	9	(3.7%)	17	(3.5%)	26	(3.6%)
VISIT 33/WEEK 120	91	(37.4%)	191	(39.8%)	282	(39.0%)
VISIT 34/WEEK 124	3	(1.2%)	3	(0.6%)	6	(0.8%)
VISIT 35/WEEK 128	3	(1.2%)	3	(0.6%)	6	(0.8%)
VISIT 36/WEEK 132	36	(14.8%)	59	(12.3%)	95	(13.1%)
VISIT 37/WEEK 136	1	(0.4%)	2	(0.4%)	3	(0.4%)
FOLLOW-UP	72	(29.6%)	118	(24.6%)	190	(26.3%)

1. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 13.3

REASON FOR CONCLUDING THE STUDY BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

CONCLUSION REASON	PRIOR TREATMENT		TOTAL (N=723)
	PLACEBO (N=243)	SB 207499 (N=480)	
ADVERSE EXPERIENCE	47 (19.3%)	69 (14.4%)	116 (16.0%)
COPD EXACERBATION	4 (1.6%)	5 (1.0%)	9 (1.2%)
INSUFFICIENT THERAPEUTIC EFFECT	1 (0.4%)	7 (1.5%)	8 (1.1%)
PROTOCOL DEVIATION (INCLUDING NON-COMPLIANCE)	5 (2.1%)	5 (1.0%)	10 (1.4%)
LOST TO FOLLOW-UP	1 (0.4%)	6 (1.3%)	7 (1.0%)
OTHER	41 (16.9%)	79 (16.5%)	120 (16.6%)
TOTAL WITHDRAWN	95 (39.1%)	166 (34.6%)	261 (36.1%)
COMPLETED STUDY	10 (4.1%)	15 (3.1%)	25 (3.5%)

1. ADVERSE EXPERIENCE ROW INCLUDES PATIENTS WITHDRAWN DUE TO COPD EXACERBATIONS
2. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 13.4

CUMULATIVE PERCENTAGE OF PATIENTS WITHDRAWN BY TIME OF WITHDRAWAL, REASON, AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

TIME (DAYS)	PLACEBO (N=243)					PRIOR TREATMENT SB 207499 (N=480)					TOTAL (N=723)				
	AE (%)	PD (%)	LTFU (%)	ITE (%)	OTHER (%)	AE (%)	PD (%)	LTFU (%)	ITE (%)	OTHER (%)	AE (%)	PD (%)	LTFU (%)	ITE (%)	OTHER (%)
<= 7	2.5	0.0	0.0	0.0	0.0	1.9	0.0	0.4	0.0	0.2	2.1	0.0	0.3	0.0	0.1
<= 14	5.8	0.4	0.0	0.0	0.4	2.1	0.0	0.4	0.0	0.6	3.3	0.1	0.3	0.0	0.6
<= 28	8.3	0.4	0.0	0.0	0.9	2.9	0.0	0.4	0.2	0.9	4.7	0.1	0.3	0.1	0.9
<= 56	9.5	0.9	0.0	0.0	2.2	4.2	0.2	0.4	0.2	1.1	6.0	0.4	0.3	0.1	1.4
<= 84	10.4	0.9	0.0	0.0	4.1	4.4	0.2	0.4	0.2	2.4	6.4	0.4	0.3	0.1	2.9
<= 112	12.6	0.9	0.0	0.0	5.0	4.9	0.2	0.4	0.4	3.0	7.4	0.4	0.3	0.3	3.7
<= 140	13.4	0.9	0.0	0.5	5.5	5.5	0.2	0.4	0.4	3.0	8.2	0.4	0.3	0.5	3.8
<= 168	13.4	0.9	0.0	0.5	6.5	5.7	0.2	0.4	0.7	3.5	8.3	0.4	0.3	0.6	4.4
<= 224	13.9	1.4	0.0	0.5	8.4	6.8	0.2	0.7	0.7	5.1	9.2	0.6	0.4	0.6	6.1
<= 280	14.4	1.4	0.0	0.5	8.9	7.3	0.5	0.7	1.2	6.0	9.7	0.8	0.4	0.9	6.9
<= 336	14.8	1.4	0.0	0.5	9.4	8.2	0.5	0.7	1.4	6.5	10.4	0.8	0.4	1.1	7.4
<= 392	15.3	1.4	0.0	0.5	11.8	8.4	0.7	0.9	1.6	9.7	10.7	0.9	0.6	1.3	10.4
<= 448	15.8	1.4	0.0	0.5	12.8	9.8	0.7	1.2	1.6	10.7	11.8	0.9	0.8	1.3	11.4
<= 504	16.3	1.4	0.0	0.5	13.9	10.6	1.0	1.4	1.6	12.1	12.5	1.1	1.0	1.3	12.7
<= 560	17.7	1.4	0.6	0.5	14.4	11.1	1.0	1.4	1.6	14.8	13.3	1.1	1.2	1.3	14.7
<= 616	17.7	1.4	0.6	0.5	15.9	12.6	1.3	1.4	1.6	15.1	14.3	1.3	1.2	1.3	15.3
<= 672	19.3	1.4	0.6	0.5	15.9	13.6	1.3	1.4	1.6	15.3	15.5	1.3	1.2	1.3	15.5
<= 728	19.8	1.4	0.6	0.5	17.0	14.5	1.3	1.4	1.6	16.4	16.3	1.3	1.2	1.3	16.6
<= 784	19.8	2.2	0.6	0.5	17.0	15.9	1.3	1.4	1.6	17.0	17.2	1.6	1.2	1.3	17.0
<= 840	20.6	3.4	0.6	0.5	21.1	15.9	1.3	1.4	1.6	19.1	17.5	2.0	1.2	1.3	19.7
<= 896	20.6	3.4	0.6	0.5	21.1	16.5	1.3	1.4	1.6	20.0	17.9	2.0	1.2	1.3	20.3
<= 952	22.7	3.4	0.6	0.5	26.3	19.3	1.3	1.4	1.6	21.2	20.4	2.0	1.2	1.3	23.0
<= 1008	22.7	3.4	0.6	0.5	26.3	19.3	1.3	1.4	1.6	21.2	20.4	2.0	1.2	1.3	23.0

1. PERCENTAGES ARE ESTIMATED USING THE KAPLAN-MEIER PRODUCT LIMIT
2. AE=ADVERSE EVENT, PD=PROTOCOL DEVIATION, LTFU=LOST TO FOLLOW-UP, ITE=INSUFFICIENT THERAPEUTIC EFFECT, OTHER=OTHER REASONS
3. TIME IS CALCULATED RELATIVE TO DAY 1 OF STUDY 040
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 13.5

SUMMARY OF CONDUCT OF STUDY DEVIATIONS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

CONDUCT OF STUDY DEVIATION	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
ENTERING INTO THE STUDY OTHER THAN THE LAST ON THERAPY VISIT DATE OF FEEDER	28 (11.5%)	48 (10.0%)	76 (10.5%)
NOT MEETING THE INCLUSION/EXCLUSION CRITERIA	2 (0.8%)	1 (0.2%)	3 (0.4%)
NOT RETURN FOR VISIT ACCORDING TO DEFINED VISIT WINDOW	195 (80.2%)	422 (87.9%)	617 (85.3%)
COMPLIANCE IS <80% OR >120% AT 2 CONSECUTIVE VISITS AFTER VISIT 1	11 (4.5%)	13 (2.7%)	24 (3.3%)
SHORT-ACTING BETA 2/ANTICHOLINERGIC or LONG ACTING BETA 2 AGONIST	53 (21.8%)	137 (28.5%)	190 (26.3%)
TESTED POSITIVE FOR PREGNANCY BUT NOT WITHDRAW	0 .	2 (0.4%)	2 (0.3%)
USED AMINOPHYLLINE AND/OR THEOPHYLLINE	5 (2.1%)	30 (6.3%)	35 (4.8%)
TOTAL	209 (86.0%)	435 (90.6%)	644 (89.1%)

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED
2. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091
3. EACH PATIENT IS COUNTED ONCE BY CONDUCT OF STUDY DEVIATION

TABLE 13.6

SUMMARY OF DEMOGRAPHIC CHARACTERISTICS AT ENTRY TO FEEDER STUDY BY PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

CHARACTERISTIC		PRIOR TREATMENT		TOTAL (N= 723)
		PLACEBO (N= 243)	SB 207499 (N= 480)	
SEX	Female	38 (15.6%)	76 (15.8%)	114 (15.8%)
	Male	205 (84.4%)	404 (84.2%)	609 (84.2%)
RACE	Caucasian	238 (97.9%)	474 (98.8%)	712 (98.5%)
	Oriental	5 (2.1%)	5 (1.0%)	10 (1.4%)
	Other	0 .	1 (0.2%)	1 (0.1%)
EMPLOYED	No	199 (81.9%)	391 (81.5%)	590 (81.6%)
	Yes	44 (18.1%)	89 (18.5%)	133 (18.4%)
AGE CATEGORY	< 50	22 (9.1%)	42 (8.8%)	64 (8.9%)
	50-65	114 (46.9%)	230 (47.9%)	344 (47.6%)
	> 65	107 (44.0%)	208 (43.3%)	315 (43.6%)
AGE (YRS)	N	243	480	723
	MEAN	63.3	62.6	62.9
	MEDIAN	64.0	64.0	64.0
	STD	9.1	8.9	9.0
	MIN	39	39	39
	MAX	84	82	84
WEIGHT (KG)	N	242	480	722
	MEAN	74.2	75.2	74.9
	MEDIAN	73.0	75.0	74.0
	STD	14.5	14.4	14.4
	MIN	44	39	39
	MAX	131	134	134
HEIGHT (CM)	N	243	480	723
	MEAN	168.7	168.7	168.7
	MEDIAN	169.0	168.0	169.0
	STD	7.9	7.9	7.9
	MIN	148	144	144
	MAX	190	190	190

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED

2. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 13.6A

SUMMARY OF DEMOGRAPHIC CHARACTERISTICS AT ENTRY TO FEEDER STUDY 042 BY PRIOR TREATMENT
 PROTOCOL 040

CHARACTERISTIC		PRIOR TREATMENT		TOTAL	
		PLACEBO (N= 143)	SB 207499 (N= 281)	(N= 424)	
SEX	Female	24 (16.8%)	49 (17.4%)	73 (17.2%)	
	Male	119 (83.2%)	232 (82.6%)	351 (82.8%)	
RACE	Caucasian	141 (98.6%)	278 (98.9%)	419 (98.8%)	
	Oriental	2 (1.4%)	2 (0.7%)	4 (0.9%)	
	Other	0 .	1 (0.4%)	1 (0.2%)	
EMPLOYED	No	122 (85.3%)	236 (84.0%)	358 (84.4%)	
	Yes	21 (14.7%)	45 (16.0%)	66 (15.6%)	
AGE CATEGORY	< 50	7 (4.9%)	18 (6.4%)	25 (5.9%)	
	50-65	66 (46.2%)	133 (47.3%)	199 (46.9%)	
	> 65	70 (49.0%)	130 (46.3%)	200 (47.2%)	
AGE (YRS)	N	143	281	424	
	MEAN	64.8	63.5	63.9	
	MEDIAN	65.0	65.0	65.0	
	STD	8.3	8.3	8.3	
	MIN	43	40	40	
	MAX	80	82	82	
WEIGHT (KG)	N	142	281	423	
	MEAN	74.3	75.1	74.8	
	MEDIAN	73.5	75.0	75.0	
	STD	15.3	13.9	14.3	
	MIN	44	39	39	
	MAX	124	134	134	
HEIGHT (CM)	N	143	281	424	
	MEAN	168.3	168.0	168.1	
	MEDIAN	168.0	168.0	168.0	
	STD	7.5	7.7	7.6	
	MIN	148	144	144	
	MAX	190	190	190	

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED FROM STUDY 042
2. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDY 042

TABLE 13.6B

SUMMARY OF DEMOGRAPHIC CHARACTERISTICS AT ENTRY TO FEEDER STUDY 091 BY PRIOR TREATMENT

PROTOCOL 040

CHARACTERISTIC		PRIOR TREATMENT		TOTAL (N= 299)
		PLACEBO (N= 100)	SB 207499 (N= 199)	
SEX	Female	14 (14.0%)	27 (13.6%)	41 (13.7%)
	Male	86 (86.0%)	172 (86.4%)	258 (86.3%)
RACE	Caucasian	97 (97.0%)	196 (98.5%)	293 (98.0%)
	Oriental	3 (3.0%)	3 (1.5%)	6 (2.0%)
EMPLOYED	No	77 (77.0%)	155 (77.9%)	232 (77.6%)
	Yes	23 (23.0%)	44 (22.1%)	67 (22.4%)
AGE CATEGORY	< 50	15 (15.0%)	24 (12.1%)	39 (13.0%)
	50-65	48 (48.0%)	97 (48.7%)	145 (48.5%)
	> 65	37 (37.0%)	78 (39.2%)	115 (38.5%)
AGE (YRS)	N	100	199	299
	MEAN	61.1	61.4	61.3
	MEDIAN	62.5	62.0	62.0
	STD	9.8	9.6	9.7
	MIN	39	39	39
	MAX	84	80	84
WEIGHT (KG)	N	100	199	299
	MEAN	74.1	75.4	75.0
	MEDIAN	72.3	74.0	74.0
	STD	13.5	15.1	14.6
	MIN	50	45	45
	MAX	131	130	131
HEIGHT (CM)	N	100	199	299
	MEAN	169.3	169.7	169.6
	MEDIAN	170.0	170.0	170.0
	STD	8.4	7.9	8.1
	MIN	149	146	146
	MAX	190	189	190

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED FROM STUDY 091
2. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDY 091

TABLE 13.7

DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION PARAMETERS* AND % PREDICTED TLCO AT ENTRY TO FEEDER STUDY
BY PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PARAMETER		PRIOR TREATMENT		TOTAL (N=723)
		PLACEBO (N=243)	SB 207499 (N=480)	

FEV1 (L)	N	243	480	723
	MEAN	1.50	1.53	1.52
	STD	0.44	0.45	0.44
	MEDIAN	1.47	1.50	1.49
	MIN	0.63	0.58	0.58
	MAX	3.46	3.24	3.46
%PREDICTED FEV1	N	243	480	723
	MEAN	49.4	50.1	49.8
	STD	11.2	11.3	11.3
	MEDIAN	49.4	49.5	49.4
	MIN	28.3	23.1	23.1
	MAX	78.6	88.2	88.2
FEV1/FVC	N	243	480	723
	MEAN	0.54	0.55	0.55
	STD	0.10	0.10	0.10
	MEDIAN	0.55	0.56	0.55
	MIN	0.30	0.25	0.25
	MAX	0.77	0.82	0.82
REVERSIBILITY (%)	N	243	480	723
	MEAN	4.9	4.8	4.8
	STD	8.6	8.7	8.7
	MEDIAN	4.9	5.4	5.2
	MIN	-25.8	-37.4	-37.4
	MAX	54.2	35.0	54.2
FVC (L)	N	243	480	723
	MEAN	2.88	2.87	2.87
	STD	0.80	0.78	0.78
	MEDIAN	2.82	2.75	2.76
	MIN	1.47	1.07	1.07
	MAX	6.04	5.72	6.04
PEFR (L/MIN)	N	243	480	723
	MEAN	205.0	209.0	207.7
	STD	73.1	74.1	73.8
	MEDIAN	196.2	196.2	196.2

* PULMONARY FUNCTION PARAMETERS INCLUDE FEV1, FVC, PEFR, FEF25-75, FEF75, FEV6, REVERSIBILITY,
% PREDICTED FEV1, AND FEV1/FVC RATIO

1. FEV1, FVC, PEFR, FEF25-75, FEF75, AND FEV6 ARE REPORTED PRE-SALBUTAMOL INHALATION

2. % PREDICTED FEV1 IS REPORTED POST-SALBUTAMOL INHALATION

3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 13.7

DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION PARAMETERS* AND % PREDICTED TLCO AT ENTRY TO FEEDER STUDY
BY PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PARAMETER		PRIOR TREATMENT		TOTAL (N=723)
		PLACEBO (N=243)	SB 207499 (N=480)	

PEFR (L/MIN)	MIN	76.8	76.8	76.8
	MAX	563.4	571.8	571.8
FEF25-75 (L/SEC)	N	243	480	723
	MEAN	0.71	0.74	0.73
	STD	0.34	0.37	0.36
	MEDIAN	0.66	0.66	0.66
	MIN	0.17	0.19	0.17
	MAX	2.32	2.52	2.52
FEF75 (L/SEC)	N	243	480	723
	MEAN	0.35	0.35	0.35
	STD	0.29	0.23	0.25
	MEDIAN	0.30	0.29	0.29
	MIN	0.08	0.06	0.06
	MAX	3.29	1.82	3.29
FEV6 (L)	N	170	326	496
	MEAN	2.70	2.65	2.67
	STD	0.69	0.71	0.70
	MEDIAN	2.67	2.55	2.59
	MIN	1.29	1.09	1.09
	MAX	4.87	4.90	4.90
%PREDICTED TLCO	N	228	456	684
	MEAN	70.3	69.4	69.7
	STD	26.4	26.4	26.4
	MEDIAN	69.0	65.8	67.1
	MIN	20.5	20.9	20.5
	MAX	186.2	185.6	186.2

* PULMONARY FUNCTION PARAMETERS INCLUDE FEV1, FVC, PEFR, FEF25-75, FEF75, FEV6, REVERSIBILITY,
% PREDICTED FEV1, AND FEV1/FVC RATIO

1. FEV1, FVC, PEFR, FEF25-75, FEF75, AND FEV6 ARE REPORTED PRE-SALBUTAMOL INHALATION

2. % PREDICTED FEV1 IS REPORTED POST-SALBUTAMOL INHALATION

3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

SB 207499

TABLE 13.7A

DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION PARAMETERS* AND % PREDICTED TLCO AT ENTRY TO FEEDER STUDY 042
BY PRIOR TREATMENT
PROTOCOL 040

PARAMETER		PRIOR TREATMENT		TOTAL (N=424)
		PLACEBO (N=143)	SB 207499 (N=281)	

FEV1 (L)	N	143	281	424
	MEAN	1.44	1.48	1.47
	STD	0.41	0.42	0.42
	MEDIAN	1.46	1.46	1.46
	MIN	0.63	0.58	0.58
	MAX	2.54	2.77	2.77
%PREDICTED FEV1	N	143	281	424
	MEAN	48.5	49.7	49.3
	STD	10.4	11.2	10.9
	MEDIAN	48.6	48.4	48.4
	MIN	28.3	23.1	23.1
	MAX	69.6	79.3	79.3
FEV1/FVC	N	143	281	424
	MEAN	0.53	0.55	0.54
	STD	0.10	0.10	0.10
	MEDIAN	0.54	0.56	0.55
	MIN	0.31	0.25	0.25
	MAX	0.70	0.82	0.82
REVERSIBILITY (%)	N	143	281	424
	MEAN	4.9	5.1	5.0
	STD	7.6	8.6	8.3
	MEDIAN	4.9	5.5	5.3
	MIN	-25.8	-36.0	-36.0
	MAX	27.0	35.0	35.0
FVC (L)	N	143	281	424
	MEAN	2.78	2.81	2.80
	STD	0.68	0.76	0.73
	MEDIAN	2.75	2.73	2.73
	MIN	1.48	1.07	1.07
	MAX	4.91	5.72	5.72
PEFR (L/MIN)	N	143	281	424
	MEAN	196.5	202.2	200.3
	STD	66.6	67.9	67.5
	MEDIAN	187.8	187.8	187.8

* PULMONARY FUNCTION PARAMETERS INCLUDE FEV1, FVC, PEFR, FEF25-75, FEF75, FEV6, REVERSIBILITY,

% PREDICTED FEV1, AND FEV1/FVC RATIO

1. FEV1, FVC, PEFR, FEF25-75, FEF75, AND FEV6 ARE REPORTED PRE-SALBUTAMOL INHALATION

2. % PREDICTED FEV1 IS REPORTED POST-SALBUTAMOL INHALATION

3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDY 042

TABLE 13.7A

DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION PARAMETERS* AND % PREDICTED TLCO AT ENTRY TO FEEDER STUDY 042
BY PRIOR TREATMENT
PROTOCOL 040

PARAMETER		PRIOR TREATMENT		TOTAL (N=424)
		PLACEBO (N=143)	SB 207499 (N=281)	

PEFR (L/MIN)	MIN	76.8	76.8	76.8
	MAX	375.6	409.8	409.8
FEF25-75 (L/SEC)	N	143	281	424
	MEAN	0.67	0.71	0.70
	STD	0.33	0.36	0.35
	MEDIAN	0.60	0.64	0.62
	MIN	0.17	0.19	0.17
	MAX	1.87	2.13	2.13
FEF75 (L/SEC)	N	143	281	424
	MEAN	0.34	0.34	0.34
	STD	0.31	0.21	0.25
	MEDIAN	0.28	0.29	0.29
	MIN	0.09	0.06	0.06
	MAX	3.29	1.56	3.29
FEV6 (L)	N	99	188	287
	MEAN	2.59	2.60	2.60
	STD	0.62	0.66	0.65
	MEDIAN	2.55	2.55	2.55
	MIN	1.29	1.09	1.09
	MAX	4.41	4.14	4.41
%PREDICTED TLCO	N	136	266	402
	MEAN	71.0	70.8	70.8
	STD	28.1	27.3	27.5
	MEDIAN	69.2	67.5	68.2
	MIN	20.5	22.8	20.5
	MAX	186.2	151.8	186.2

* PULMONARY FUNCTION PARAMETERS INCLUDE FEV1, FVC, PEFR, FEF25-75, FEF75, FEV6, REVERSIBILITY,
% PREDICTED FEV1, AND FEV1/FVC RATIO

1. FEV1, FVC, PEFR, FEF25-75, FEF75, AND FEV6 ARE REPORTED PRE-SALBUTAMOL INHALATION

2. % PREDICTED FEV1 IS REPORTED POST-SALBUTAMOL INHALATION

3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDY 042

SB 207499

TABLE 13.7B

DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION PARAMETERS* AND % PREDICTED TLCO AT ENTRY TO FEEDER STUDY 091
BY PRIOR TREATMENT
PROTOCOL 040

PARAMETER		PRIOR TREATMENT		TOTAL (N=299)
		PLACEBO (N=100)	SB 207499 (N=199)	

FEV1 (L)	N	100	199	299
	MEAN	1.58	1.59	1.59
	STD	0.48	0.47	0.47
	MEDIAN	1.51	1.55	1.54
	MIN	0.63	0.72	0.63
	MAX	3.46	3.24	3.46
%PREDICTED FEV1	N	100	199	299
	MEAN	50.7	50.6	50.6
	STD	12.3	11.5	11.8
	MEDIAN	50.6	50.8	50.7
	MIN	28.8	24.9	24.9
	MAX	78.6	88.2	88.2
FEV1/FVC	N	100	199	299
	MEAN	0.55	0.56	0.56
	STD	0.11	0.10	0.10
	MEDIAN	0.56	0.55	0.55
	MIN	0.30	0.28	0.28
	MAX	0.77	0.76	0.77
REVERSIBILITY (%)	N	100	199	299
	MEAN	4.7	4.5	4.6
	STD	9.9	8.9	9.3
	MEDIAN	4.7	5.2	4.8
	MIN	-21.6	-37.4	-37.4
	MAX	54.2	31.9	54.2
FVC (L)	N	100	199	299
	MEAN	3.02	2.94	2.97
	STD	0.92	0.80	0.84
	MEDIAN	2.88	2.76	2.83
	MIN	1.47	1.44	1.44
	MAX	6.04	5.65	6.04
PEFR (L/MIN)	N	100	199	299
	MEAN	217.1	218.7	218.1
	STD	80.4	81.2	80.8
	MEDIAN	204.6	204.6	204.6

* PULMONARY FUNCTION PARAMETERS INCLUDE FEV1, FVC, PEFR, FEF25-75, FEF75, FEV6, REVERSIBILITY,

% PREDICTED FEV1, AND FEV1/FVC RATIO

1. FEV1, FVC, PEFR, FEF25-75, FEF75, AND FEV6 ARE REPORTED PRE-SALBUTAMOL INHALATION

2. % PREDICTED FEV1 IS REPORTED POST-SALBUTAMOL INHALATION

3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDY 091

SB 207499

TABLE 13.7B

DESCRIPTIVE STATISTICS FOR PULMONARY FUNCTION PARAMETERS* AND % PREDICTED TLCO AT ENTRY TO FEEDER STUDY 091
BY PRIOR TREATMENT
PROTOCOL 040

PARAMETER		PRIOR TREATMENT		TOTAL (N=299)
		PLACEBO (N=100)	SB 207499 (N=199)	

PEFR (L/MIN)	MIN	76.8	76.8	76.8
	MAX	563.4	571.8	571.8
FEF25-75 (L/SEC)	N	100	199	299
	MEAN	0.76	0.78	0.77
	STD	0.36	0.38	0.38
	MEDIAN	0.70	0.71	0.70
	MIN	0.20	0.20	0.20
	MAX	2.32	2.52	2.52
FEF75 (L/SEC)	N	100	199	299
	MEAN	0.36	0.36	0.36
	STD	0.28	0.25	0.26
	MEDIAN	0.33	0.29	0.31
	MIN	0.08	0.09	0.08
	MAX	2.48	1.82	2.48
FEV6 (L)	N	71	138	209
	MEAN	2.85	2.73	2.77
	STD	0.74	0.76	0.75
	MEDIAN	2.82	2.58	2.69
	MIN	1.39	1.33	1.33
	MAX	4.87	4.90	4.90
%PREDICTED TLCO	N	92	190	282
	MEAN	69.3	67.6	68.1
	STD	23.8	25.0	24.6
	MEDIAN	68.6	64.4	66.6
	MIN	29.3	20.9	20.9
	MAX	143.2	185.6	185.6

* PULMONARY FUNCTION PARAMETERS INCLUDE FEV1, FVC, PEFR, FEF25-75, FEF75, FEV6, REVERSIBILITY,
% PREDICTED FEV1, AND FEV1/FVC RATIO

1. FEV1, FVC, PEFR, FEF25-75, FEF75, AND FEV6 ARE REPORTED PRE-SALBUTAMOL INHALATION

2. % PREDICTED FEV1 IS REPORTED POST-SALBUTAMOL INHALATION

3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDY 091

TABLE 13.8

DESCRIPTIVE STATISTICS FOR SMOKING HISTORY, ALCOHOL INTAKE AND DURATION OF COPD AT ENTRY TO FEEDER STUDY BY
PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PARAMETER		PRIOR TREATMENT		TOTAL (N=723)
		PLACEBO (N=243)	SB 207499 (N=480)	
SMOKER STATUS	PREVIOUS SMOKER	143 (58.8%)	266 (55.4%)	409 (56.6%)
	CURRENT SMOKER	100 (41.2%)	214 (44.6%)	314 (43.4%)
PACK YEARS	N	243	479	722
	MEAN	43.7	44.8	44.4
	STD	22.2	23.0	22.7
	MEDIAN	40.0	40.0	40.0
	MIN	10.0	10.0	10.0
	MAX	150.0	153.0	153.0
CIGARETTES/DAY	N	100	214	314
	MEAN	17.5	18.0	17.8
	STD	11.5	10.5	10.8
	MEDIAN	17.0	20.0	18.0
	MIN	2.0	1.0	1.0
	MAX	60.0	40.0	60.0
ALCOHOL INTAKE (UNITS/WEEK)	N	242	478	720
	MEAN	6.5	6.2	6.3
	STD	9.6	9.2	9.3
	MEDIAN	2.0	2.0	2.0
	MIN	0.0	0.0	0.0
	MAX	56.0	70.0	70.0
DURATION COPD (YEARS)	N	242	479	721
	MEAN	8.5	8.7	8.7
	STD	8.4	8.4	8.4
	MEDIAN	6.0	6.0	6.0
	MIN	0.0	0.0	0.0
	MAX	44.0	55.0	55.0

1. SAMPLE SIZE IS BASED ON NUMBER OF PATIENTS ENROLLED
2. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 13.8A

DESCRIPTIVE STATISTICS FOR SMOKING HISTORY, ALCOHOL INTAKE AND DURATION OF COPD AT ENTRY TO FEEDER STUDY 042
BY PRIOR TREATMENT
PROTOCOL 040

PARAMETER		PRIOR TREATMENT		TOTAL (N=424)
		PLACEBO (N=143)	SB 207499 (N=281)	
SMOKER STATUS	PREVIOUS SMOKER	87 (60.8%)	158 (56.2%)	245 (57.8%)
	CURRENT SMOKER	56 (39.2%)	123 (43.8%)	179 (42.2%)
PACK YEARS	N	143	281	424
	MEAN	46.0	46.2	46.1
	STD	23.4	24.1	23.8
	MEDIAN	45.0	40.0	42.5
	MIN	10.0	10.0	10.0
	MAX	150.0	153.0	153.0
CIGARETTES/DAY	N	56	123	179
	MEAN	17.3	16.7	16.9
	STD	12.8	10.2	11.1
	MEDIAN	15.0	15.0	15.0
	MIN	2.0	1.0	1.0
	MAX	60.0	40.0	60.0
ALCOHOL INTAKE (UNITS/WEEK)	N	142	281	423
	MEAN	5.9	5.8	5.8
	STD	9.3	9.1	9.2
	MEDIAN	2.0	2.0	2.0
	MIN	0.0	0.0	0.0
	MAX	56.0	70.0	70.0
DURATION COPD (YEARS)	N	142	280	422
	MEAN	8.6	8.2	8.3
	STD	9.1	8.1	8.4
	MEDIAN	5.0	5.0	5.0
	MIN	0.0	0.0	0.0
	MAX	44.0	51.0	51.0

1. SAMPLE SIZE IS BASED ON NUMBER OF PATIENTS ENROLLED FROM STUDY 042
2. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDY 042

TABLE 13.8B

DESCRIPTIVE STATISTICS FOR SMOKING HISTORY, ALCOHOL INTAKE AND DURATION OF COPD AT ENTRY TO FEEDER STUDY 091
BY PRIOR TREATMENT
PROTOCOL 040

PARAMETER		PRIOR TREATMENT		TOTAL (N=299)
		PLACEBO (N=100)	SB 207499 (N=199)	
SMOKER STATUS	PREVIOUS SMOKER	56 (56.0%)	108 (54.3%)	164 (54.8%)
	CURRENT SMOKER	44 (44.0%)	91 (45.7%)	135 (45.2%)
PACK YEARS	N	100	198	298
	MEAN	40.3	42.8	42.0
	STD	20.0	21.2	20.8
	MEDIAN	35.0	40.0	38.9
	MIN	10.0	10.0	10.0
	MAX	123.0	100.0	123.0
CIGARETTES/DAY	N	44	91	135
	MEAN	17.9	19.6	19.1
	STD	9.7	10.7	10.4
	MEDIAN	20.0	20.0	20.0
	MIN	4.0	1.0	1.0
	MAX	40.0	40.0	40.0
ALCOHOL INTAKE (UNITS/WEEK)	N	100	197	297
	MEAN	7.5	6.9	7.1
	STD	9.8	9.3	9.5
	MEDIAN	5.0	3.0	4.0
	MIN	0.0	0.0	0.0
	MAX	56.0	50.0	56.0
DURATION COPD (YEARS)	N	100	199	299
	MEAN	8.4	9.6	9.2
	STD	7.4	8.9	8.4
	MEDIAN	6.5	7.0	7.0
	MIN	0.0	0.0	0.0
	MAX	35.0	55.0	55.0

1. SAMPLE SIZE IS BASED ON NUMBER OF PATIENTS ENROLLED FROM STUDY 091
2. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDY 091

TABLE 13.9A

SUMMARY OF PRIOR MEDICAL CONDITIONS AT SCREENING BY DISEASE CLASS LEVEL, PREFERRED TERM, AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

DISEASE CLASS LEVEL 1	PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
TOTAL	TOTAL	182 (74.9%)	357 (74.4%)	539 (74.6%)
ANOMALIES	TOTAL	0 .	2 (0.4%)	2 (0.3%)
	CONG ANOM, GI	0 .	1 (0.2%)	1 (0.1%)
	CONG ANOM, OTHER	0 .	1 (0.2%)	1 (0.1%)
BLOOD/BLOOD FORMING ORGAN DIS	TOTAL	2 (0.8%)	2 (0.4%)	4 (0.6%)
	ANEMIA, IRON DEFIC	2 (0.8%)	0 .	2 (0.3%)
	ANEMIA, OTHER	0 .	1 (0.2%)	1 (0.1%)
	LEUCOCYTOSIS	0 .	1 (0.2%)	1 (0.1%)
CIRCULATORY SYST	TOTAL	37 (15.2%)	69 (14.4%)	106 (14.7%)
	ANEURYSM, AORTIC	1 (0.4%)	3 (0.6%)	4 (0.6%)
	ANEURYSM, NOT AORTIC	1 (0.4%)	1 (0.2%)	2 (0.3%)
	ANGINA PECTORIS	2 (0.8%)	4 (0.8%)	6 (0.8%)
	ARRHYTHMIA	1 (0.4%)	2 (0.4%)	3 (0.4%)
	ARTERIAL DISORD, OTHER	2 (0.8%)	1 (0.2%)	3 (0.4%)
	ATHEROSCLEROSIS	1 (0.4%)	2 (0.4%)	3 (0.4%)
	CEREBRAL ARTERY OCCLUSION	0 .	1 (0.2%)	1 (0.1%)
	CEREBROVASCULAR DIS	1 (0.4%)	9 (1.9%)	10 (1.4%)
	CIRCULATORY SYST DISORD	0 .	1 (0.2%)	1 (0.1%)
	CONDUCTION DISORD	0 .	1 (0.2%)	1 (0.1%)
	EMBOLISM/THROMBOSIS, VENOUS	0 .	2 (0.4%)	2 (0.3%)
	EXTRASYSTOLES	0 .	1 (0.2%)	1 (0.1%)
	FIBRILLATION, ATRIAL	0 .	2 (0.4%)	2 (0.3%)
	FLUTTER, ATRIAL	1 (0.4%)	3 (0.6%)	4 (0.6%)
	HEART FAILURE	2 (0.8%)	3 (0.6%)	5 (0.7%)
	HEMORRHAGE, INTRACRANIAL	0 .	2 (0.4%)	2 (0.3%)
	HEMORRHOIDS	2 (0.8%)	6 (1.3%)	8 (1.1%)
	HYPERTENSION	1 (0.4%)	5 (1.0%)	6 (0.8%)
	ISCHEMIC HEART DIS	0 .	2 (0.4%)	2 (0.3%)
	MITRAL VALVE DISORD	0 .	1 (0.2%)	1 (0.1%)
	MYOCARDIAL INFARCTION	14 (5.8%)	14 (2.9%)	28 (3.9%)
	MYOCARDIAL INFARCTION, OLD	0 .	3 (0.6%)	3 (0.4%)
	PERICARDITIS, ACUTE	1 (0.4%)	1 (0.2%)	2 (0.3%)
	PERIPH VASCULAR DIS	0 .	3 (0.6%)	3 (0.4%)
	PHLEBITIS	3 (1.2%)	3 (0.6%)	6 (0.8%)
	PULM EMBOLISM AND INFARCT	5 (2.1%)	2 (0.4%)	7 (1.0%)
	RHEUMATIC FEVER	1 (0.4%)	1 (0.2%)	2 (0.3%)

1. PERCENTAGES ARE BASED ON TOTAL NUMBER OF PATIENTS ENROLLED

2. EXCLUSIVELY PRIOR CONDITIONS-ONGOING CONDITIONS SUMMARIZED IN TABLE 13.9B

3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 13.9A

SUMMARY OF PRIOR MEDICAL CONDITIONS AT SCREENING BY DISEASE CLASS LEVEL, PREFERRED TERM, AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

DISEASE CLASS LEVEL 1	PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
CIRCULATORY SYST	TACHYCARDIA	0 .	1 (0.2%)	1 (0.1%)
	SUPRAVENTRICULAR TRANSIENT CEREBRAL ISCHEMIA	0 .	6 (1.3%)	6 (0.8%)
	VARICES	4 (1.6%)	1 (0.2%)	5 (0.7%)
	TOTAL	1 (0.4%)	0 .	1 (0.1%)
COMPLIC OF PREGNANCY/BIRTH	PREGNANCY, COMPLICATIONS	1 (0.4%)	0 .	1 (0.1%)
	TOTAL	1 (0.4%)	0 .	1 (0.1%)
DIGESTIVE SYST	TOTAL	54 (22.2%)	104 (21.7%)	158 (21.9%)
	ANAL	1 (0.4%)	5 (1.0%)	6 (0.8%)
	FISSURE/FISTULA/ABSCCESS			
	APPENDICITIS	1 (0.4%)	3 (0.6%)	4 (0.6%)
	CHOLELITHIASIS	0 .	2 (0.4%)	2 (0.3%)
	DIGESTIVE DISORD, OTHER	2 (0.8%)	0 .	2 (0.3%)
	DIVERTICULITIS	1 (0.4%)	0 .	1 (0.1%)
	DYSPEPSIA	3 (1.2%)	3 (0.6%)	6 (0.8%)
	ENTERITIS/COLITIS	1 (0.4%)	2 (0.4%)	3 (0.4%)
	ESOPHAGITIS	3 (1.2%)	6 (1.3%)	9 (1.2%)
	ESOPHAGUS DIS	2 (0.8%)	0 .	2 (0.3%)
	GALLBLADDER DISORD, OTHER	0 .	3 (0.6%)	3 (0.4%)
	GASTRITIS/DUODENITIS	4 (1.6%)	9 (1.9%)	13 (1.8%)
	HEMORRHAGE, GI	3 (1.2%)	3 (0.6%)	6 (0.8%)
	HEPATITIS	4 (1.6%)	6 (1.3%)	10 (1.4%)
	HEPATOBI DIS	1 (0.4%)	1 (0.2%)	2 (0.3%)
	HERNIA, ABDOMINAL	8 (3.3%)	15 (3.1%)	23 (3.2%)
	INTEST DISORD, OTHER	1 (0.4%)	1 (0.2%)	2 (0.3%)
	INTEST OBSTRUCTION	0 .	5 (1.0%)	5 (0.7%)
	LIVER DISORD	0 .	3 (0.6%)	3 (0.4%)
	MELENA	1 (0.4%)	0 .	1 (0.1%)
	ORAL SOFT TISSUE DIS	0 .	2 (0.4%)	2 (0.3%)
	PANCREATITIS	1 (0.4%)	2 (0.4%)	3 (0.4%)
	PERITONEAL DISORD, OTHER	0 .	1 (0.2%)	1 (0.1%)
	PERITONITIS	1 (0.4%)	2 (0.4%)	3 (0.4%)
	POLYPS, ANAL/RECTAL	1 (0.4%)	2 (0.4%)	3 (0.4%)
	STOMACH/DUODENUM DISORD	0 .	1 (0.2%)	1 (0.1%)
	ULCER, DUODENAL	13 (5.3%)	28 (5.8%)	41 (5.7%)
	ULCER, GASTRIC	9 (3.7%)	7 (1.5%)	16 (2.2%)
	ULCER, PEPTIC, OTHER	4 (1.6%)	7 (1.5%)	11 (1.5%)
ENDOCR/METAB/IMMUNITY DISORD	TOTAL	7 (2.9%)	11 (2.3%)	18 (2.5%)

1. PERCENTAGES ARE BASED ON TOTAL NUMBER OF PATIENTS ENROLLED
2. EXCLUSIVELY PRIOR CONDITIONS-ONGOING CONDITIONS SUMMARIZED IN TABLE 13.9B
3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 13.9A

SUMMARY OF PRIOR MEDICAL CONDITIONS AT SCREENING BY DISEASE CLASS LEVEL, PREFERRED TERM, AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

DISEASE CLASS LEVEL 1	PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
ENDOCR/METAB/IMMUNITY DISORD	CHOLEST/TRIGLYCERIDE, ELEVATED	1 (0.4%)	5 (1.0%)	6 (0.8%)
	GOITER	1 (0.4%)	2 (0.4%)	3 (0.4%)
	GOUT	3 (1.2%)	1 (0.2%)	4 (0.6%)
	HYPERALIMENTATION	0 .	1 (0.2%)	1 (0.1%)
	HYPERLIPEMIA	1 (0.4%)	0 .	1 (0.1%)
	HYPERTHYROIDISM	2 (0.8%)	0 .	2 (0.3%)
	PLASMA PROTEIN DISORD	0 .	1 (0.2%)	1 (0.1%)
	VITAMIN D DEFIC	0 .	1 (0.2%)	1 (0.1%)
EXT CAUSES OF INJURY/POISONING	TOTAL	2 (0.8%)	4 (0.8%)	6 (0.8%)
	ACCIDENT/MOTOR VEHICLE	0 .	1 (0.2%)	1 (0.1%)
	ADVERSE EFF/ANALGESIC	0 .	1 (0.2%)	1 (0.1%)
	ADVERSE EFF/ANTIBIOTIC	0 .	1 (0.2%)	1 (0.1%)
	ADVERSE EFF/HORMONE	1 (0.4%)	0 .	1 (0.1%)
	POISONING	1 (0.4%)	0 .	1 (0.1%)
	SUICIDE	0 .	1 (0.2%)	1 (0.1%)
FAMILY/PERSONAL HISTORY	TOTAL	1 (0.4%)	3 (0.6%)	4 (0.6%)
	MANAGEMENT, CONTRACEPTIVE NEED/OTHER PROPHYLAXIS	1 (0.4%)	2 (0.4%)	3 (0.4%)
		0 .	1 (0.2%)	1 (0.1%)
GENITOURINARY SYST DIS	TOTAL	29 (11.9%)	27 (5.6%)	56 (7.7%)
	BREAST DISORD	2 (0.8%)	2 (0.4%)	4 (0.6%)
	GENITAL FEMALE DISORD, OTHER	2 (0.8%)	8 (1.7%)	10 (1.4%)
	GENITAL MALE DISORD, OTHER	5 (2.1%)	4 (0.8%)	9 (1.2%)
	GYNECOMASTIA	0 .	1 (0.2%)	1 (0.1%)
	HEMATURIA	3 (1.2%)	2 (0.4%)	5 (0.7%)
	INFLAM PELVIC DIS	0 .	1 (0.2%)	1 (0.1%)
	KIDNEY DISORD	1 (0.4%)	0 .	1 (0.1%)
	KIDNEY INFECT	0 .	2 (0.4%)	2 (0.3%)
	KIDNEY/URETER, CALCULUS	4 (1.6%)	6 (1.3%)	10 (1.4%)
	MENOPAUSAL STATES	3 (1.2%)	2 (0.4%)	5 (0.7%)
	POSTMENOPAUSAL BLEEDING	0 .	1 (0.2%)	1 (0.1%)
	PROSTATE DISORD	7 (2.9%)	2 (0.4%)	9 (1.2%)
	RENAL FAILURE	1 (0.4%)	0 .	1 (0.1%)
	RENAL FAILURE, ACUTE	1 (0.4%)	0 .	1 (0.1%)
	URINARY TRACT INFECTION	2 (0.8%)	2 (0.4%)	4 (0.6%)
INFECTIOUS/PARASITIC DIS	TOTAL	34 (14.0%)	58 (12.1%)	92 (12.7%)

1. PERCENTAGES ARE BASED ON TOTAL NUMBER OF PATIENTS ENROLLED

2. EXCLUSIVELY PRIOR CONDITIONS-ONGOING CONDITIONS SUMMARIZED IN TABLE 13.9B

3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 13.9A

SUMMARY OF PRIOR MEDICAL CONDITIONS AT SCREENING BY DISEASE CLASS LEVEL, PREFERRED TERM, AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

DISEASE CLASS LEVEL 1	PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
INFECTIOUS/PARASITIC DIS	ARTHROPOD-BORNE DIS, OTHER	2 (0.8%)	1 (0.2%)	3 (0.4%)
	BACT DIS, OTHER	1 (0.4%)	2 (0.4%)	3 (0.4%)
	HEPATITIS, VIRAL	1 (0.4%)	4 (0.8%)	5 (0.7%)
	HEPATITIS, VIRAL	2 (0.8%)	0	2 (0.3%)
	INFECT/PARASIT DIS, LATE EFF	0	1 (0.2%)	1 (0.1%)
	INFECTION, SKIN	1 (0.4%)	0	1 (0.1%)
	INTEST INFECT DIS	0	3 (0.6%)	3 (0.4%)
	MYCOSES	2 (0.8%)	1 (0.2%)	3 (0.4%)
	POLIO AND CNS DIS, VIRAL	0	1 (0.2%)	1 (0.1%)
	SALMONELLA INFECT	1 (0.4%)	0	1 (0.1%)
	TUBERCULOSIS	23 (9.5%)	41 (8.5%)	64 (8.9%)
	TYPHOID INFECT	1 (0.4%)	1 (0.2%)	2 (0.3%)
	VIRAL DIS/EXANTHEM	3 (1.2%)	3 (0.6%)	6 (0.8%)
	VIRAL INFECTION	1 (0.4%)	0	1 (0.1%)
	VIRUS/CHLAMYD DIS, OTHER	0	3 (0.6%)	3 (0.4%)
	ZOONOTIC BACT DIS	1 (0.4%)	3 (0.6%)	4 (0.6%)
INJURY/POISONING	TOTAL	19 (7.8%)	48 (10.0%)	67 (9.3%)
	ALLERGIC REACTION, FOOD	0	1 (0.2%)	1 (0.1%)
	DISLOCATION	0	1 (0.2%)	1 (0.1%)
	FRACTURE, BONE UNSPEC	1 (0.4%)	0	1 (0.1%)
	FRACTURE, LOWER LIMB	10 (4.1%)	11 (2.3%)	21 (2.9%)
	FRACTURE, NECK/TRUNK	3 (1.2%)	19 (4.0%)	22 (3.0%)
	FRACTURE, UPPER LIMB	7 (2.9%)	10 (2.1%)	17 (2.4%)
	INJURY, CHEST/ABD/PELV	0	1 (0.2%)	1 (0.1%)
	INJURY, INTRACRANIAL	1 (0.4%)	2 (0.4%)	3 (0.4%)
	INJURY, NERV, SP CD	1 (0.4%)	0	1 (0.1%)
	INJURY/POIS, OTHER	1 (0.4%)	0	1 (0.1%)
	OPEN WOUND	0	1 (0.2%)	1 (0.1%)
	POISONING, DRUG, MEDICINAL	0	1 (0.2%)	1 (0.1%)
	TRAUMA/INJURIES, UNSPEC	2 (0.8%)	8 (1.7%)	10 (1.4%)
	TRAUMATIC AMPUTATION	0	2 (0.4%)	2 (0.3%)
MENTAL DISORD	TOTAL	27 (11.1%)	41 (8.5%)	68 (9.4%)
	ALCOHOL ABUSE	1 (0.4%)	1 (0.2%)	2 (0.3%)
	ALCOHOLIC DEPEND	2 (0.8%)	1 (0.2%)	3 (0.4%)
	ANXIETY	6 (2.5%)	5 (1.0%)	11 (1.5%)
	DEPRESSION	4 (1.6%)	11 (2.3%)	15 (2.1%)
	TOBACCO USE	14 (5.8%)	28 (5.8%)	42 (5.8%)

1. PERCENTAGES ARE BASED ON TOTAL NUMBER OF PATIENTS ENROLLED

2. EXCLUSIVELY PRIOR CONDITIONS-ONGOING CONDITIONS SUMMARIZED IN TABLE 13.9B

3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 13.9A

SUMMARY OF PRIOR MEDICAL CONDITIONS AT SCREENING BY DISEASE CLASS LEVEL, PREFERRED TERM, AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

DISEASE CLASS LEVEL 1	PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
MUSCULOSKEL/CONNECT TISSUE DIS	TOTAL	19 (7.8%)	28 (5.8%)	47 (6.5%)
	ARTHROPATHY	2 (0.8%)	3 (0.6%)	5 (0.7%)
	BACK PAIN	4 (1.6%)	8 (1.7%)	12 (1.7%)
	BONE INFECT	0 .	2 (0.4%)	2 (0.3%)
	BONE/CARTIL DISORD, OTHER	1 (0.4%)	1 (0.2%)	2 (0.3%)
	CERVICAL DISORD, OTHER	0 .	1 (0.2%)	1 (0.1%)
	INTERVERTEB DISC, ABN	2 (0.8%)	4 (0.8%)	6 (0.8%)
	JOINT DISORD, OTHER	1 (0.4%)	1 (0.2%)	2 (0.3%)
	JOINT, DERANGEMENT	0 .	1 (0.2%)	1 (0.1%)
	NEURALGIA, BACK	4 (1.6%)	0 .	4 (0.6%)
	OSTEOARTHRISIS	1 (0.4%)	3 (0.6%)	4 (0.6%)
	OSTEOCHONDROPATHIES	0 .	1 (0.2%)	1 (0.1%)
	PAIN, JOINT	0 .	1 (0.2%)	1 (0.1%)
	PAIN, LIMB	1 (0.4%)	0 .	1 (0.1%)
	PAIN, NECK	0 .	1 (0.2%)	1 (0.1%)
	RHEUMATIC DISORD	6 (2.5%)	2 (0.4%)	8 (1.1%)
	SOFT TISSUE DISORD	1 (0.4%)	1 (0.2%)	2 (0.3%)
NEOPLASMS	TOTAL	9 (3.7%)	29 (6.0%)	38 (5.3%)
	CARCINOMA IN SITU	0 .	1 (0.2%)	1 (0.1%)
	NEOPLASM MALIG, BREAST	0 .	1 (0.2%)	1 (0.1%)
	NEOPLASM MALIG, DIGEST ORG	0 .	3 (0.6%)	3 (0.4%)
	NEOPLASM MALIG, GU	1 (0.4%)	1 (0.2%)	2 (0.3%)
	NEOPLASM MALIG, ORAL	0 .	1 (0.2%)	1 (0.1%)
	NEOPLASM MALIG, OTHER SITES	0 .	2 (0.4%)	2 (0.3%)
	NEOPLASM MALIG, RESP/INTRATHOR	2 (0.8%)	2 (0.4%)	4 (0.6%)
	NEOPLASM MALIG, SKIN	1 (0.4%)	4 (0.8%)	5 (0.7%)
	NEOPLASM, UNSPEC	3 (1.2%)	1 (0.2%)	4 (0.6%)
	NEOPLASMS BENIGN	2 (0.8%)	12 (2.5%)	14 (1.9%)
	NEOPLASMS, UNCERT BEHAV	0 .	2 (0.4%)	2 (0.3%)
NERVOUS SYST/SENSE ORGAN DIS	TOTAL	15 (6.2%)	21 (4.4%)	36 (5.0%)
	AUT NERV SYST DISORD	0 .	1 (0.2%)	1 (0.1%)
	CATARACT	3 (1.2%)	0 .	3 (0.4%)
	CONJUNCTIVAL DISORD	0 .	2 (0.4%)	2 (0.3%)
	EAR/MASTOID DISORD	3 (1.2%)	5 (1.0%)	8 (1.1%)
	EPILEPSY	0 .	1 (0.2%)	1 (0.1%)
	EYE DISORD, OTHER	2 (0.8%)	2 (0.4%)	4 (0.6%)
	GLAUCOMA	2 (0.8%)	1 (0.2%)	3 (0.4%)

1. PERCENTAGES ARE BASED ON TOTAL NUMBER OF PATIENTS ENROLLED
2. EXCLUSIVELY PRIOR CONDITIONS-ONGOING CONDITIONS SUMMARIZED IN TABLE 13.9B
3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 13.9A

SUMMARY OF PRIOR MEDICAL CONDITIONS AT SCREENING BY DISEASE CLASS LEVEL, PREFERRED TERM, AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

DISEASE CLASS LEVEL 1	PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
NERVOUS SYST/SENSE ORGAN DIS	HEARING LOSS	0	1 (0.2%)	1 (0.1%)
	MIGRAINE	0	1 (0.2%)	1 (0.1%)
	OPTIC NERVE DISORD	0	1 (0.2%)	1 (0.1%)
	OTITIS MEDIA	1 (0.4%)	1 (0.2%)	2 (0.3%)
	PERIPH NERV SYST DISORD	1 (0.4%)	3 (0.6%)	4 (0.6%)
	RETINAL DISORD	3 (1.2%)	1 (0.2%)	4 (0.6%)
	TINNITUS	0	1 (0.2%)	1 (0.1%)
	VISION ABNORMAL	1 (0.4%)	0	1 (0.1%)
OPERATIONS	TOTAL	106 (43.6%)	190 (39.6%)	296 (40.9%)
	OPERATION, ANUS	4 (1.6%)	5 (1.0%)	9 (1.2%)
	OPERATION, APPENDIX	19 (7.8%)	43 (9.0%)	62 (8.6%)
	OPERATION, BONE/JOINT	10 (4.1%)	22 (4.6%)	32 (4.4%)
	OPERATION, BREAST	2 (0.8%)	3 (0.6%)	5 (0.7%)
	OPERATION, CNS	2 (0.8%)	3 (0.6%)	5 (0.7%)
	OPERATION, EAR	3 (1.2%)	7 (1.5%)	10 (1.4%)
	OPERATION, ENDOCR	2 (0.8%)	5 (1.0%)	7 (1.0%)
	OPERATION, ESOPHAGUS	1 (0.4%)	0	1 (0.1%)
	OPERATION, EYE	8 (3.3%)	8 (1.7%)	16 (2.2%)
	OPERATION, FEM GENITAL	4 (1.6%)	18 (3.8%)	22 (3.0%)
	OPERATION, GB	6 (2.5%)	19 (4.0%)	25 (3.5%)
	OPERATION, HEART VESSELS	4 (1.6%)	5 (1.0%)	9 (1.2%)
	OPERATION, HERNIA REPAIR	27 (11.1%)	30 (6.3%)	57 (7.9%)
	OPERATION, INTEST	3 (1.2%)	7 (1.5%)	10 (1.4%)
	OPERATION, KIDNEY	3 (1.2%)	2 (0.4%)	5 (0.7%)
	OPERATION, LYMPH	1 (0.4%)	1 (0.2%)	2 (0.3%)
	OPERATION, MALE GENITAL	17 (7.0%)	17 (3.5%)	34 (4.7%)
	OPERATION, MUSCLE/TENDON	2 (0.8%)	6 (1.3%)	8 (1.1%)
	OPERATION, NOSE/MOUTH	14 (5.8%)	29 (6.0%)	43 (5.9%)
	OPERATION, OTHER ABDOM	1 (0.4%)	1 (0.2%)	2 (0.3%)
	OPERATION, OTHER HEART	0	1 (0.2%)	1 (0.1%)
	OPERATION, OTHER	2 (0.8%)	1 (0.2%)	3 (0.4%)
	MUSCULOSKEL			
	OPERATION, OTHER URINARY	2 (0.8%)	1 (0.2%)	3 (0.4%)
	OPERATION, OTHER VESSELS	9 (3.7%)	20 (4.2%)	29 (4.0%)
	OPERATION,	2 (0.8%)	4 (0.8%)	6 (0.8%)
	RECTUM/PERIRECT			
	OPERATION, RESP	5 (2.1%)	18 (3.8%)	23 (3.2%)
	OPERATION, SKIN/SUBCUT	3 (1.2%)	5 (1.0%)	8 (1.1%)
	OPERATION, SOFT TISSUE	0	1 (0.2%)	1 (0.1%)
	OPERATION, STOMACH	6 (2.5%)	7 (1.5%)	13 (1.8%)
	OPERATION/STOMACH	1 (0.4%)	1 (0.2%)	2 (0.3%)

1. PERCENTAGES ARE BASED ON TOTAL NUMBER OF PATIENTS ENROLLED
2. EXCLUSIVELY PRIOR CONDITIONS-ONGOING CONDITIONS SUMMARIZED IN TABLE 13.9B
3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 13.9A

SUMMARY OF PRIOR MEDICAL CONDITIONS AT SCREENING BY DISEASE CLASS LEVEL, PREFERRED TERM, AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

DISEASE CLASS LEVEL 1	PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
OPERATIONS	PROCEDURE, SURGERY UNSP	0 .	3 (0.6%)	3 (0.4%)
PROCEDURES	TOTAL	2 (0.8%)	5 (1.0%)	7 (1.0%)
	EVALUATION, DX EXAM	1 (0.4%)	1 (0.2%)	2 (0.3%)
	PROCEDURE, NUCLEAR	0 .	1 (0.2%)	1 (0.1%)
	MEDICINE			
	PROCEDURES, OTHER	0 .	1 (0.2%)	1 (0.1%)
	NONOPERATIVE			
	RADIOLOGY, DIAGNOSTIC	1 (0.4%)	0 .	1 (0.1%)
	THERAPY, REHAB	0 .	2 (0.4%)	2 (0.3%)
RESPIRATORY SYST DIS	TOTAL	49 (20.2%)	106 (22.1%)	155 (21.4%)
	ASTHMA	9 (3.7%)	16 (3.3%)	25 (3.5%)
	BRONCHITIS, ACUTE	3 (1.2%)	1 (0.2%)	4 (0.6%)
	BRONCHITIS, CHRONIC	2 (0.8%)	6 (1.3%)	8 (1.1%)
	BRONCHITIS, OTHER	1 (0.4%)	4 (0.8%)	5 (0.7%)
	EMPHYSEMA	0 .	1 (0.2%)	1 (0.1%)
	EMPYEMA	3 (1.2%)	2 (0.4%)	5 (0.7%)
	FAILURE, RESP	0 .	1 (0.2%)	1 (0.1%)
	INFECTION, RESP	1 (0.4%)	2 (0.4%)	3 (0.4%)
	INFLUENZA	0 .	1 (0.2%)	1 (0.1%)
	LUNG DIS, OBSTRUCTIVE	0 .	2 (0.4%)	2 (0.3%)
	LUNG DIS, OTHER	5 (2.1%)	8 (1.7%)	13 (1.8%)
	NASAL POLYPS	0 .	1 (0.2%)	1 (0.1%)
	PHARYNGITIS, ACUTE	0 .	3 (0.6%)	3 (0.4%)
	PLEURISY	4 (1.6%)	19 (4.0%)	23 (3.2%)
	PNEUMONIA, BACT	0 .	3 (0.6%)	3 (0.4%)
	PNEUMONIA, OTHER	19 (7.8%)	38 (7.9%)	57 (7.9%)
	PNEUMONIA, VIRAL	0 .	1 (0.2%)	1 (0.1%)
	PNEUMOTHORAX	10 (4.1%)	8 (1.7%)	18 (2.5%)
	RESP DIS, OTHER	1 (0.4%)	4 (0.8%)	5 (0.7%)
	RHINITIS, ALLERGIC	0 .	3 (0.6%)	3 (0.4%)
	RHINITIS,NOS	1 (0.4%)	1 (0.2%)	2 (0.3%)
	SINUSITIS, OTHER	0 .	1 (0.2%)	1 (0.1%)
	SINUSITIS,NOS	3 (1.2%)	3 (0.6%)	6 (0.8%)
	UPPER RESP DIS, OTHER	2 (0.8%)	4 (0.8%)	6 (0.8%)
	UPPER RESP DISORD, OTHER	0 .	1 (0.2%)	1 (0.1%)
	UPPER RESP INFECT, ACUTE	0 .	2 (0.4%)	2 (0.3%)
SIGNS, SYMPTOMS, ILL-DEFINED CON	TOTAL	22 (9.1%)	49 (10.2%)	71 (9.8%)
	APNEA	0 .	2 (0.4%)	2 (0.3%)

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3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 13.9A

SUMMARY OF PRIOR MEDICAL CONDITIONS AT SCREENING BY DISEASE CLASS LEVEL, PREFERRED TERM, AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

DISEASE CLASS LEVEL 1	PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
SIGNS, SYMPTOMS, ILL-DEFINED CON	CARDIOVAS FUNCTIONS/ECG, ABN	1 (0.4%)	2 (0.4%)	3 (0.4%)
	DIARRHEA	1 (0.4%)	0	1 (0.1%)
	DISTURBANCE, VOICE	1 (0.4%)	2 (0.4%)	3 (0.4%)
	DIZZINESS AND GIDDINESS	1 (0.4%)	2 (0.4%)	3 (0.4%)
	DYSURIA	1 (0.4%)	1 (0.2%)	2 (0.3%)
	EDEMA	0	1 (0.2%)	1 (0.1%)
	EPISTAXIS	1 (0.4%)	1 (0.2%)	2 (0.3%)
	FLATULENCE	1 (0.4%)	0	1 (0.1%)
	HEADACHE	3 (1.2%)	4 (0.8%)	7 (1.0%)
	HEARTBURN	1 (0.4%)	1 (0.2%)	2 (0.3%)
	HEMOPTYSIS	2 (0.8%)	7 (1.5%)	9 (1.2%)
	INCONTINENCE, URINARY	1 (0.4%)	0	1 (0.1%)
	LYMPHADENOPATHY	0	1 (0.2%)	1 (0.1%)
	MALAISE AND FATIGUE	1 (0.4%)	0	1 (0.1%)
	PAIN UNSP, CHEST	2 (0.8%)	3 (0.6%)	5 (0.7%)
	PAIN, ABDOMINO-PELVIC	5 (2.1%)	6 (1.3%)	11 (1.5%)
	PAIN, GENERAL	0	1 (0.2%)	1 (0.1%)
	PALPITATIONS	0	3 (0.6%)	3 (0.4%)
	POLYURIA	0	1 (0.2%)	1 (0.1%)
	PYREXIA	1 (0.4%)	0	1 (0.1%)
	RADIOLOGY INTRATHORACIC, ABN	0	2 (0.4%)	2 (0.3%)
	RENAL COLIC	2 (0.8%)	6 (1.3%)	8 (1.1%)
	SERUM GLUCOSE, ELEVATED	0	3 (0.6%)	3 (0.4%)
	SERUM URIC ACID, ELEVATED	1 (0.4%)	4 (0.8%)	5 (0.7%)
	SPUTUM, ABN	0	1 (0.2%)	1 (0.1%)
	SWELLING/MASS, HEAD, NECK	1 (0.4%)	1 (0.2%)	2 (0.3%)
	SYNCOPE AND COLLAPSE	2 (0.8%)	1 (0.2%)	3 (0.4%)
	TETANY	0	1 (0.2%)	1 (0.1%)
	WEIGHT LOSS	1 (0.4%)	1 (0.2%)	2 (0.3%)
SKIN/SUBCUTANEOUS TISSUE DIS	TOTAL	5 (2.1%)	13 (2.7%)	18 (2.5%)
	ALOPECIA	0	1 (0.2%)	1 (0.1%)
	CELLULITIS/ABSCCESS	0	1 (0.2%)	1 (0.1%)
	CYST, PILONIDAL	0	1 (0.2%)	1 (0.1%)
	CYST, SEBACEOUS	0	1 (0.2%)	1 (0.1%)
	INFLAM SKIN/SUBCUT	2 (0.8%)	6 (1.3%)	8 (1.1%)
	SKIN/SUBCUT DISORD, OTHER	3 (1.2%)	2 (0.4%)	5 (0.7%)
	URTICARIA	0	1 (0.2%)	1 (0.1%)

1. PERCENTAGES ARE BASED ON TOTAL NUMBER OF PATIENTS ENROLLED
2. EXCLUSIVELY PRIOR CONDITIONS-ONGOING CONDITIONS SUMMARIZED IN TABLE 13.9B
3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 13.9B

SUMMARY OF CURRENT/ACTIVE MEDICAL CONDITIONS AT SCREENING BY DISEASE CLASS LEVEL, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

DISEASE CLASS LEVEL 1	PREFERRED TERM	PLACEBO (N=243)		PRIOR TREATMENT SB 207499 (N=480)		Total (N=723)	
TOTAL	TOTAL	243	(100.0%)	480	(100.0%)	723	(100.0%)
ANOMALIES	TOTAL	4	(1.6%)	4	(0.8%)	8	(1.1%)
	CHROMOSOMAL ANOM	0	.	1	(0.2%)	1	(0.1%)
	CONG ANOM, CIRC SYST	1	(0.4%)	1	(0.2%)	2	(0.3%)
	CONG ANOM, GU	1	(0.4%)	0	.	1	(0.1%)
	CONG ANOM, HEART	1	(0.4%)	0	.	1	(0.1%)
	CONG ANOM, MUSCULOSKEL	1	(0.4%)	1	(0.2%)	2	(0.3%)
	CONGEN ANOM, HEAD/NECK	0	.	1	(0.2%)	1	(0.1%)
BLOOD/BLOOD FORMING ORGAN DIS	TOTAL	7	(2.9%)	16	(3.3%)	23	(3.2%)
	ANEMIA, IRON DEFIC	0	.	1	(0.2%)	1	(0.1%)
	ANEMIA, OTHER	5	(2.1%)	1	(0.2%)	6	(0.8%)
	ANEMIA, PERNICIOUS	0	.	1	(0.2%)	1	(0.1%)
	BLOOD DIS, OTHER	1	(0.4%)	1	(0.2%)	2	(0.3%)
	COAGULATION DEFECTS	0	.	1	(0.2%)	1	(0.1%)
	EOSINOPHILIA	0	.	1	(0.2%)	1	(0.1%)
	ERYTHROCYTOSIS	0	.	2	(0.4%)	2	(0.3%)
	LEUCOCYTOSIS	1	(0.4%)	1	(0.2%)	2	(0.3%)
	LYMPHOCYTOSIS	0	.	1	(0.2%)	1	(0.1%)
	POLYCYTHEMIA	0	.	5	(1.0%)	5	(0.7%)
	THROMBOCYTOPENIA	1	(0.4%)	2	(0.4%)	3	(0.4%)
CIRCULATORY SYST	TOTAL	112	(46.1%)	207	(43.1%)	319	(44.1%)
	ANEURYSM, AORTIC	0	.	2	(0.4%)	2	(0.3%)
	ANGINA PECTORIS	7	(2.9%)	13	(2.7%)	20	(2.8%)
	AORTIC VALVE DISORD	0	.	1	(0.2%)	1	(0.1%)
	ARRHYTHMIA	1	(0.4%)	11	(2.3%)	12	(1.7%)
	ARTERIAL DISORD, OTHER	2	(0.8%)	5	(1.0%)	7	(1.0%)
	ARTERITIS	3	(1.2%)	8	(1.7%)	11	(1.5%)
	ATHEROSCLEROSIS	3	(1.2%)	1	(0.2%)	4	(0.6%)
	ATHEROSCLEROSIS, HEART	1	(0.4%)	2	(0.4%)	3	(0.4%)
	AV BLOCK	1	(0.4%)	5	(1.0%)	6	(0.8%)
	BRADYCARDIA	1	(0.4%)	1	(0.2%)	2	(0.3%)
	CARDIOMEGALY	2	(0.8%)	10	(2.1%)	12	(1.7%)
	CARDIOMYOPATHY, PRIMARY	1	(0.4%)	0	.	1	(0.1%)
	CEREBROVASCULAR DIS	3	(1.2%)	5	(1.0%)	8	(1.1%)
	CIRCULATORY SYST DISORD	7	(2.9%)	7	(1.5%)	14	(1.9%)
	CONDUCTION DISORD	11	(4.5%)	19	(4.0%)	30	(4.1%)
	EXTRASYSTOLES	0	.	1	(0.2%)	1	(0.1%)
	EXTRASYSTOLES, ATRIAL	2	(0.8%)	0	.	2	(0.3%)

1. PERCENTAGES ARE BASED ON TOTAL NUMBER OF PATIENTS ENROLLED

2. CURRENT/ACTIVE CONDITIONS - EXCLUSIVELY PRIOR CONDITIONS SUMMARIZED IN TABLE 13.9A

3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 13.9B

SUMMARY OF CURRENT/ACTIVE MEDICAL CONDITIONS AT SCREENING BY DISEASE CLASS LEVEL, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

DISEASE CLASS LEVEL 1	PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
CIRCULATORY SYST	EXTRASYSTOLES, VENTRICULAR	0 .	3 (0.6%)	3 (0.4%)
	FIBRILLATION	0 .	1 (0.2%)	1 (0.1%)
	FIBRILLATION, ATRIAL	6 (2.5%)	7 (1.5%)	13 (1.8%)
	FLUTTER, ATRIAL	1 (0.4%)	1 (0.2%)	2 (0.3%)
	HEART DIS, OTHER	0 .	1 (0.2%)	1 (0.1%)
	HEART FAILURE	4 (1.6%)	14 (2.9%)	18 (2.5%)
	HEMORRHOIDS	0 .	5 (1.0%)	5 (0.7%)
	HYPERTENSION	61 (25.1%)	117 (24.4%)	178 (24.6%)
	HYPERTENSION, PULMONARY	0 .	1 (0.2%)	1 (0.1%)
	HYPOTENSION, OTHER	0 .	2 (0.4%)	2 (0.3%)
	ISCHEMIC HEART DIS	18 (7.4%)	27 (5.6%)	45 (6.2%)
	MITRAL VALVE DISORD	0 .	1 (0.2%)	1 (0.1%)
	MYOCARDIAL INFARCTION	4 (1.6%)	1 (0.2%)	5 (0.7%)
	PERIPH VASCULAR DIS	7 (2.9%)	6 (1.3%)	13 (1.8%)
	PRECEREBRAL ARTERY OCCLUSION	1 (0.4%)	1 (0.2%)	2 (0.3%)
	PULM HEART DIS, CHRONIC	2 (0.8%)	5 (1.0%)	7 (1.0%)
	TACHYCARDIA	0 .	5 (1.0%)	5 (0.7%)
	SUPRAVENTRICULAR			
	VALVULAR HEART DISEASE, NOS	1 (0.4%)	2 (0.4%)	3 (0.4%)
	VARICES	1 (0.4%)	9 (1.9%)	10 (1.4%)
DIGESTIVE SYST	TOTAL	31 (12.8%)	70 (14.6%)	101 (14.0%)
	CHOLELITHIASIS	1 (0.4%)	4 (0.8%)	5 (0.7%)
	CONSTIPATION	2 (0.8%)	4 (0.8%)	6 (0.8%)
	DIVERTICULITIS	3 (1.2%)	1 (0.2%)	4 (0.6%)
	DYSPEPSIA	10 (4.1%)	9 (1.9%)	19 (2.6%)
	ENTERITIS/COLITIS	0 .	2 (0.4%)	2 (0.3%)
	ESOPHAGITIS	2 (0.8%)	8 (1.7%)	10 (1.4%)
	ESOPHAGUS DIS	0 .	2 (0.4%)	2 (0.3%)
	GASTRITIS/DUODENITIS	0 .	10 (2.1%)	10 (1.4%)
	HERNIA, ABDOMINAL	11 (4.5%)	23 (4.8%)	34 (4.7%)
	INTEST DISORD, OTHER	0 .	1 (0.2%)	1 (0.1%)
	INTEST MALABSORPTION	1 (0.4%)	0 .	1 (0.1%)
	LIVER DISORD	0 .	5 (1.0%)	5 (0.7%)
	PANCREATITIS	1 (0.4%)	0 .	1 (0.1%)
	PERIODONTAL DIS	0 .	1 (0.2%)	1 (0.1%)
	STOMACH/DUODENUM DISORD	0 .	1 (0.2%)	1 (0.1%)
	TEETH DISORD	0 .	1 (0.2%)	1 (0.1%)
	ULCER, DUODENAL	2 (0.8%)	5 (1.0%)	7 (1.0%)

1. PERCENTAGES ARE BASED ON TOTAL NUMBER OF PATIENTS ENROLLED

2. CURRENT/ACTIVE CONDITIONS - EXCLUSIVELY PRIOR CONDITIONS SUMMARIZED IN TABLE 13.9A

3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 13.9B

SUMMARY OF CURRENT/ACTIVE MEDICAL CONDITIONS AT SCREENING BY DISEASE CLASS LEVEL, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

DISEASE CLASS LEVEL 1	PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
DIGESTIVE SYST	ULCER, GASTRIC	0	1 (0.2%)	1 (0.1%)
	ULCER, PEPTIC, OTHER	1 (0.4%)	2 (0.4%)	3 (0.4%)
ENDOCR/METAB/IMMUNITY DISORD	TOTAL	53 (21.8%)	105 (21.9%)	158 (21.9%)
	ADRENAL DEFIC	0	1 (0.2%)	1 (0.1%)
	AMINO-ACID DISORD	0	1 (0.2%)	1 (0.1%)
	CARBOHYDRATE DISORD	0	1 (0.2%)	1 (0.1%)
	CHOLEST/TRIGLYCERIDE, ELEVATED	30 (12.3%)	33 (6.9%)	63 (8.7%)
	CUSHING'S SYNDROME	0	1 (0.2%)	1 (0.1%)
	DIABETES MELLITUS	15 (6.2%)	34 (7.1%)	49 (6.8%)
	GOITER	1 (0.4%)	5 (1.0%)	6 (0.8%)
	GOUT	1 (0.4%)	5 (1.0%)	6 (0.8%)
	HYPERLIPEMIA	3 (1.2%)	9 (1.9%)	12 (1.7%)
	HYPERPROTEINEMIA	1 (0.4%)	0	1 (0.1%)
	HYPERTHYROIDISM	0	1 (0.2%)	1 (0.1%)
	HYPOTHYROIDISM	1 (0.4%)	6 (1.3%)	7 (1.0%)
	LIPID METAB DISORD	0	2 (0.4%)	2 (0.3%)
	METAB DISORD, OTHER	0	2 (0.4%)	2 (0.3%)
	OBESITY	9 (3.7%)	22 (4.6%)	31 (4.3%)
	PARATHYROID DISORD	1 (0.4%)	0	1 (0.1%)
	PLASMA PROTEIN DISORD	1 (0.4%)	0	1 (0.1%)
	SERUM POTASSIUM, DECREASED	0	1 (0.2%)	1 (0.1%)
	VITAMIN B DEFIC	0	2 (0.4%)	2 (0.3%)
	VITAMIN D DEFIC	0	1 (0.2%)	1 (0.1%)
	VITAMIN DEFIC, OTHER	0	1 (0.2%)	1 (0.1%)
EXT CAUSES OF INJURY/POISONING	TOTAL	12 (4.9%)	15 (3.1%)	27 (3.7%)
	ADVERSE EFF/ANALGESIC	2 (0.8%)	2 (0.4%)	4 (0.6%)
	ADVERSE EFF/ANTI-INFECT	1 (0.4%)	2 (0.4%)	3 (0.4%)
	ADVERSE EFF/ANTIBIOTIC	7 (2.9%)	8 (1.7%)	15 (2.1%)
	ADVERSE EFF/HORMONE	1 (0.4%)	0	1 (0.1%)
	ADVERSE EFF/OTHER DRUG	0	1 (0.2%)	1 (0.1%)
	ADVERSE EFF/RESP AGENT	0	1 (0.2%)	1 (0.1%)
	ADVERSE EFF/SKIN,MUC	0	1 (0.2%)	1 (0.1%)
	MEMB DRUG			
	POISONING	1 (0.4%)	0	1 (0.1%)
	SUICIDE	0	1 (0.2%)	1 (0.1%)
FAMILY/PERSONAL HISTORY	TOTAL	0	3 (0.6%)	3 (0.4%)
	STATUS, POSTSURGICAL	0	3 (0.6%)	3 (0.4%)

1. PERCENTAGES ARE BASED ON TOTAL NUMBER OF PATIENTS ENROLLED

2. CURRENT/ACTIVE CONDITIONS - EXCLUSIVELY PRIOR CONDITIONS SUMMARIZED IN TABLE 13.9A

3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 13.9B

SUMMARY OF CURRENT/ACTIVE MEDICAL CONDITIONS AT SCREENING BY DISEASE CLASS LEVEL, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

DISEASE CLASS LEVEL 1	PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
GENITOURINARY SYST DIS	TOTAL	37 (15.2%)	53 (11.0%)	90 (12.4%)
	CYSTITIS	0 .	1 (0.2%)	1 (0.1%)
	GENITAL FEMALE DISORD, OTHER	5 (2.1%)	2 (0.4%)	7 (1.0%)
	GENITAL MALE DISORD, OTHER	0 .	2 (0.4%)	2 (0.3%)
	GLOMERULONEPHRITIS	0 .	2 (0.4%)	2 (0.3%)
	HEMATURIA	4 (1.6%)	5 (1.0%)	9 (1.2%)
	INCONTINENCE, STRESS	0 .	1 (0.2%)	1 (0.1%)
	KIDNEY DISORD	1 (0.4%)	1 (0.2%)	2 (0.3%)
	KIDNEY/URETER, CALCULUS	0 .	3 (0.6%)	3 (0.4%)
	MENOPAUSAL STATES	11 (4.5%)	12 (2.5%)	23 (3.2%)
	PROSTATE DISORD	14 (5.8%)	24 (5.0%)	38 (5.3%)
	RENAL FAILURE	0 .	1 (0.2%)	1 (0.1%)
	URINARY TRACT INFECTION	3 (1.2%)	3 (0.6%)	6 (0.8%)
INFECTIOUS/PARASITIC DIS	TOTAL	3 (1.2%)	3 (0.6%)	6 (0.8%)
	INFECT/PARASIT DIS, LATE EFF	1 (0.4%)	0 .	1 (0.1%)
	MYCOSES	1 (0.4%)	1 (0.2%)	2 (0.3%)
	TUBERCULOSIS	0 .	1 (0.2%)	1 (0.1%)
	VIRAL DIS/EXANTHEM	1 (0.4%)	1 (0.2%)	2 (0.3%)
INJURY/POISONING	TOTAL	1 (0.4%)	6 (1.3%)	7 (1.0%)
	ALLERGY, NEC	0 .	3 (0.6%)	3 (0.4%)
	FRACTURE, NECK/TRUNK	0 .	1 (0.2%)	1 (0.1%)
	INJURY, CRUSHING	0 .	1 (0.2%)	1 (0.1%)
	MOTION SICKNESS	1 (0.4%)	0 .	1 (0.1%)
	SPRAINS/STRAINS	0 .	1 (0.2%)	1 (0.1%)
MENTAL DISORD	TOTAL	26 (10.7%)	62 (12.9%)	88 (12.2%)
	ANXIETY	3 (1.2%)	11 (2.3%)	14 (1.9%)
	DEPRESSION	8 (3.3%)	21 (4.4%)	29 (4.0%)
	IMPOTENCE	4 (1.6%)	3 (0.6%)	7 (1.0%)
	NEUROSES	1 (0.4%)	3 (0.6%)	4 (0.6%)
	PSYCHOSES, AFFECTIVE	1 (0.4%)	1 (0.2%)	2 (0.3%)
	PSYCHOSES, SENILE	0 .	1 (0.2%)	1 (0.1%)
	TOBACCO USE	10 (4.1%)	27 (5.6%)	37 (5.1%)
MUSCULOSKEL/CONNECT TISSUE DIS	TOTAL	52 (21.4%)	103 (21.5%)	155 (21.4%)
	ARTHRITIS, RHEUMATOID	2 (0.8%)	2 (0.4%)	4 (0.6%)
	ARTHROPATHY	5 (2.1%)	6 (1.3%)	11 (1.5%)

1. PERCENTAGES ARE BASED ON TOTAL NUMBER OF PATIENTS ENROLLED

2. CURRENT/ACTIVE CONDITIONS - EXCLUSIVELY PRIOR CONDITIONS SUMMARIZED IN TABLE 13.9A

3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 13.9B

SUMMARY OF CURRENT/ACTIVE MEDICAL CONDITIONS AT SCREENING BY DISEASE CLASS LEVEL, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

DISEASE CLASS LEVEL 1	PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
MUSCULOSKEL/CONNECT TISSUE DIS	BACK DISORD, OTHER	0	3 (0.6%)	3 (0.4%)
	BACK PAIN	6 (2.5%)	10 (2.1%)	16 (2.2%)
	BONE DEFORM, OTHER	0	3 (0.6%)	3 (0.4%)
	BONE/CARTIL DISORD, OTHER	4 (1.6%)	7 (1.5%)	11 (1.5%)
	CERVICAL DISORD, OTHER	2 (0.8%)	2 (0.4%)	4 (0.6%)
	CONNECT TISSUE DIS	1 (0.4%)	0	1 (0.1%)
	CRAMP, LIMB	1 (0.4%)	1 (0.2%)	2 (0.3%)
	DEFORMITY, ACQUIRED	0	8 (1.7%)	8 (1.1%)
	INTERVERTEB DISC, ABN	2 (0.8%)	5 (1.0%)	7 (1.0%)
	MYALGIA	1 (0.4%)	3 (0.6%)	4 (0.6%)
	NEURALGIA	0	1 (0.2%)	1 (0.1%)
	NEURALGIA, BACK	3 (1.2%)	4 (0.8%)	7 (1.0%)
	OSTEOARTHRISIS	25 (10.3%)	34 (7.1%)	59 (8.2%)
	OSTEOCHONDROPATHIES	0	1 (0.2%)	1 (0.1%)
	PAIN, JOINT	2 (0.8%)	1 (0.2%)	3 (0.4%)
	PAIN, LIMB	1 (0.4%)	2 (0.4%)	3 (0.4%)
	PAIN, NECK	1 (0.4%)	1 (0.2%)	2 (0.3%)
	RHEUMATIC DISORD	1 (0.4%)	2 (0.4%)	3 (0.4%)
	SOFT TISSUE DISORD	2 (0.8%)	3 (0.6%)	5 (0.7%)
	SPASM, MUSCLE	2 (0.8%)	4 (0.8%)	6 (0.8%)
	SPONDYLOPATHY, INFLAM	1 (0.4%)	2 (0.4%)	3 (0.4%)
	SPONDYLOSIS	11 (4.5%)	26 (5.4%)	37 (5.1%)
	SWELLING, LIMB	1 (0.4%)	0	1 (0.1%)
NEOPLASMS	TOTAL	4 (1.6%)	5 (1.0%)	9 (1.2%)
	CARCINOMA IN SITU	1 (0.4%)	0	1 (0.1%)
	NEOPLASM MALIG, BREAST	1 (0.4%)	0	1 (0.1%)
	NEOPLASM MALIG, GU	1 (0.4%)	1 (0.2%)	2 (0.3%)
	NEOPLASM MALIG,	0	1 (0.2%)	1 (0.1%)
	LYMPH/HEMAT			
NERVOUS SYST/SENSE ORGAN DIS	NEOPLASMS BENIGN	1 (0.4%)	3 (0.6%)	4 (0.6%)
	TOTAL	17 (7.0%)	48 (10.0%)	65 (9.0%)
	AUT NERV SYST DISORD	0	1 (0.2%)	1 (0.1%)
	CATARACT	1 (0.4%)	7 (1.5%)	8 (1.1%)
	EAR/MASTOID DISORD	0	6 (1.3%)	6 (0.8%)
	EPILEPSY	3 (1.2%)	3 (0.6%)	6 (0.8%)
	EXTRAPYRAMID DISORD	0	3 (0.6%)	3 (0.4%)
	EYE DISORD, OTHER	1 (0.4%)	3 (0.6%)	4 (0.6%)
	GLAUCOMA	0	8 (1.7%)	8 (1.1%)
	HEARING LOSS	8 (3.3%)	14 (2.9%)	22 (3.0%)
	LACRIMATION DISORD	0	1 (0.2%)	1 (0.1%)

1. PERCENTAGES ARE BASED ON TOTAL NUMBER OF PATIENTS ENROLLED

2. CURRENT/ACTIVE CONDITIONS - EXCLUSIVELY PRIOR CONDITIONS SUMMARIZED IN TABLE 13.9A

3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 13.9B

SUMMARY OF CURRENT/ACTIVE MEDICAL CONDITIONS AT SCREENING BY DISEASE CLASS LEVEL, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

DISEASE CLASS LEVEL 1	PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
NERVOUS SYST/SENSE ORGAN DIS	MIGRAINE	1 (0.4%)	3 (0.6%)	4 (0.6%)
	OCCCLUSION, RETINAL ARTERY	0 .	1 (0.2%)	1 (0.1%)
	OTITIS MEDIA	0 .	1 (0.2%)	1 (0.1%)
	PARALYSIS, OTHER	1 (0.4%)	0 .	1 (0.1%)
	PARKINSON'S DIS	1 (0.4%)	0 .	1 (0.1%)
	PERIPH NERV SYST DISORD	1 (0.4%)	2 (0.4%)	3 (0.4%)
	RETINAL DISORD	0 .	1 (0.2%)	1 (0.1%)
	RETINOPATHY, DIABETIC	0 .	1 (0.2%)	1 (0.1%)
	TINNITUS	0 .	1 (0.2%)	1 (0.1%)
	VISION ABNORMAL	1 (0.4%)	0 .	1 (0.1%)
	VISUAL DISTURB	0 .	1 (0.2%)	1 (0.1%)
OPERATIONS	TOTAL	6 (2.5%)	8 (1.7%)	14 (1.9%)
	OPERATION, BONE MARROW/SPLEEN	0 .	1 (0.2%)	1 (0.1%)
	OPERATION, BONE/JOINT	0 .	3 (0.6%)	3 (0.4%)
	OPERATION, EYE	0 .	1 (0.2%)	1 (0.1%)
	OPERATION, FEM GENITAL	0 .	1 (0.2%)	1 (0.1%)
	OPERATION, GB	1 (0.4%)	0 .	1 (0.1%)
	OPERATION, HEART VESSELS	1 (0.4%)	1 (0.2%)	2 (0.3%)
	OPERATION, MALE GENITAL	1 (0.4%)	0 .	1 (0.1%)
	OPERATION, OTHER HEART	3 (1.2%)	1 (0.2%)	4 (0.6%)
PROCEDURES	TOTAL	0 .	1 (0.2%)	1 (0.1%)
	RADIOLOGY, DIAGNOSTIC	0 .	1 (0.2%)	1 (0.1%)
RESPIRATORY SYST DIS	TOTAL	243 (100.0%)	480 (100.0%)	723 (100.0%)
	ASTHMA	0 .	3 (0.6%)	3 (0.4%)
	BRONCHITIS, CHRONIC	26 (10.7%)	49 (10.2%)	75 (10.4%)
	BRONCHITIS, OTHER	0 .	4 (0.8%)	4 (0.6%)
	BRONCHOPNEUMONIA	1 (0.4%)	0 .	1 (0.1%)
	EMPHYSEMA	22 (9.1%)	36 (7.5%)	58 (8.0%)
	LUNG DIS, OBSTRUCTIVE	243 (100.0%)	480 (100.0%)	723 (100.0%)
	LUNG DIS, OTHER	4 (1.6%)	13 (2.7%)	17 (2.4%)
	LUNG DIS/EXTERNAL AGENT	2 (0.8%)	5 (1.0%)	7 (1.0%)
	NASAL POLYPS	0 .	1 (0.2%)	1 (0.1%)
	PHARYNGITIS, ACUTE	2 (0.8%)	0 .	2 (0.3%)
	PLEURISY	2 (0.8%)	6 (1.3%)	8 (1.1%)
	RESP DIS, OTHER	3 (1.2%)	2 (0.4%)	5 (0.7%)
	RHINITIS, ALLERGIC	1 (0.4%)	10 (2.1%)	11 (1.5%)
	RHINITIS, CHRONIC	1 (0.4%)	6 (1.3%)	7 (1.0%)
	RHINITIS,NOS	0 .	1 (0.2%)	1 (0.1%)

1. PERCENTAGES ARE BASED ON TOTAL NUMBER OF PATIENTS ENROLLED

2. CURRENT/ACTIVE CONDITIONS - EXCLUSIVELY PRIOR CONDITIONS SUMMARIZED IN TABLE 13.9A

3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 13.9B

SUMMARY OF CURRENT/ACTIVE MEDICAL CONDITIONS AT SCREENING BY DISEASE CLASS LEVEL, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

DISEASE CLASS LEVEL 1	PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
RESPIRATORY SYST DIS	SINUSITIS, CHRONIC	2 (0.8%)	5 (1.0%)	7 (1.0%)
	SINUSITIS, OTHER	2 (0.8%)	4 (0.8%)	6 (0.8%)
	SINUSITIS,NOS	2 (0.8%)	1 (0.2%)	3 (0.4%)
	UPPER RESP DISORD, OTHER	1 (0.4%)	1 (0.2%)	2 (0.3%)
SIGNS,SYMPTOMS,ILL-DEFINED CON	TOTAL	64 (26.3%)	110 (22.9%)	174 (24.1%)
	ABNORMALITIES, RESP	1 (0.4%)	2 (0.4%)	3 (0.4%)
	ANOREXIA	0	1 (0.2%)	1 (0.1%)
	APNEA	2 (0.8%)	7 (1.5%)	9 (1.2%)
	CARDIOVAS FUNCTIONS/ECG, ABN	6 (2.5%)	6 (1.3%)	12 (1.7%)
	COUGH	1 (0.4%)	2 (0.4%)	3 (0.4%)
	DIARRHEA	0	2 (0.4%)	2 (0.3%)
	DISTURBANCE, SLEEP, UNSPEC	2 (0.8%)	1 (0.2%)	3 (0.4%)
	DISTURBANCE, VOICE	0	1 (0.2%)	1 (0.1%)
	DIZZINESS AND GIDDINESS	3 (1.2%)	4 (0.8%)	7 (1.0%)
	DYSPHAGIA	1 (0.4%)	1 (0.2%)	2 (0.3%)
	DYSPNEA, OTHER	1 (0.4%)	3 (0.6%)	4 (0.6%)
	EDEMA	1 (0.4%)	6 (1.3%)	7 (1.0%)
	FLATULENCE	1 (0.4%)	0	1 (0.1%)
	FLUSHING	1 (0.4%)	0	1 (0.1%)
	GLYCOSURIA	1 (0.4%)	1 (0.2%)	2 (0.3%)
	HEADACHE	1 (0.4%)	12 (2.5%)	13 (1.8%)
	HEARTBURN	2 (0.8%)	6 (1.3%)	8 (1.1%)
	HEPATOMEGALY	1 (0.4%)	0	1 (0.1%)
	HYPOXIA	2 (0.8%)	1 (0.2%)	3 (0.4%)
	INCONTINENCE, URINARY	1 (0.4%)	1 (0.2%)	2 (0.3%)
	INSOMNIA	12 (4.9%)	13 (2.7%)	25 (3.5%)
	LIVER FUNC TESTS/ENZY, ABNORM	0	1 (0.2%)	1 (0.1%)
	LYMPHADENOPATHY	0	1 (0.2%)	1 (0.1%)
	MASS, ABDOMINO-PELVIC	0	1 (0.2%)	1 (0.1%)
	MENTAL STATUS, IMPAIRED	1 (0.4%)	1 (0.2%)	2 (0.3%)
	NAUSEA AND VOMITING	0	1 (0.2%)	1 (0.1%)
	NERVOUSNESS	0	1 (0.2%)	1 (0.1%)
	PAIN UNSP, CHEST	0	3 (0.6%)	3 (0.4%)
	PAIN, ABDOMINO-PELVIC	2 (0.8%)	5 (1.0%)	7 (1.0%)
	PAIN, RESP	0	1 (0.2%)	1 (0.1%)
	PARESTHESIA	2 (0.8%)	0	2 (0.3%)
	PROTEINURIA	2 (0.8%)	5 (1.0%)	7 (1.0%)

1. PERCENTAGES ARE BASED ON TOTAL NUMBER OF PATIENTS ENROLLED

2. CURRENT/ACTIVE CONDITIONS - EXCLUSIVELY PRIOR CONDITIONS SUMMARIZED IN TABLE 13.9A

3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 13.9B

SUMMARY OF CURRENT/ACTIVE MEDICAL CONDITIONS AT SCREENING BY DISEASE CLASS LEVEL, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

DISEASE CLASS LEVEL 1	PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
SIGNS, SYMPTOMS, ILL-DEFINED CON	RADIOLOGY INTRATHORACIC, ABN	2 (0.8%)	2 (0.4%)	4 (0.6%)
	RADIOLOGY LUNG, ABN	2 (0.8%)	1 (0.2%)	3 (0.4%)
	RASH/OTHER SKIN ERUPTION	0 .	1 (0.2%)	1 (0.1%)
	RENAL COLIC	1 (0.4%)	1 (0.2%)	2 (0.3%)
	RESP CHEST SOUNDS, ABN	1 (0.4%)	8 (1.7%)	9 (1.2%)
	RESP SYMPTOMS, OTHER	0 .	3 (0.6%)	3 (0.4%)
	RESPIRATORY, ABN	1 (0.4%)	0 .	1 (0.1%)
	RETENTION, URINARY	1 (0.4%)	0 .	1 (0.1%)
	SERUM BILIRUBIN, INCREASED	1 (0.4%)	0 .	1 (0.1%)
	SERUM GLUCOSE, ELEVATED	3 (1.2%)	4 (0.8%)	7 (1.0%)
	SERUM URIC ACID, ELEVATED	17 (7.0%)	15 (3.1%)	32 (4.4%)
	TACHYCARDIA, UNSPEC	1 (0.4%)	2 (0.4%)	3 (0.4%)
	TRANSAMINASE/LDH, ELEVATION	4 (1.6%)	9 (1.9%)	13 (1.8%)
	TREMOR	0 .	1 (0.2%)	1 (0.1%)
	WEAKNESS	0 .	1 (0.2%)	1 (0.1%)
	WEIGHT LOSS	0 .	1 (0.2%)	1 (0.1%)
	WHEEZING	1 (0.4%)	3 (0.6%)	4 (0.6%)
SKIN/SUBCUTANEOUS TISSUE DIS	TOTAL	15 (6.2%)	28 (5.8%)	43 (5.9%)
	INFLAM SKIN/SUBCUT	12 (4.9%)	21 (4.4%)	33 (4.6%)
	PRURITUS DISORD, UNSPEC	1 (0.4%)	0 .	1 (0.1%)
	SKIN/SUBCUT DISORD, OTHER	1 (0.4%)	4 (0.8%)	5 (0.7%)
	ULCER, SKIN	0 .	1 (0.2%)	1 (0.1%)
	URTICARIA	1 (0.4%)	2 (0.4%)	3 (0.4%)

1. PERCENTAGES ARE BASED ON TOTAL NUMBER OF PATIENTS ENROLLED
2. CURRENT/ACTIVE CONDITIONS - EXCLUSIVELY PRIOR CONDITIONS SUMMARIZED IN TABLE 13.9A
3. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 13.10A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
TOTAL	230 (94.7%)	456 (95.0%)	686 (94.9%)
SALBUTAMOL	212 (87.2%)	398 (82.9%)	610 (84.4%)
IPRATROPIUM BROMIDE	95 (39.1%)	180 (37.5%)	275 (38.0%)
ACETYLSALICYLIC ACID	24 (9.9%)	42 (8.8%)	66 (9.1%)
PARACETAMOL	20 (8.2%)	34 (7.1%)	54 (7.5%)
HYDROCHLOROTHIAZIDE	10 (4.1%)	22 (4.6%)	32 (4.4%)
OMEPRAZOLE	9 (3.7%)	18 (3.8%)	27 (3.7%)
ALLOPURINOL	11 (4.5%)	15 (3.1%)	26 (3.6%)
NIFEDIPINE	6 (2.5%)	18 (3.8%)	24 (3.3%)
GLYCERYL TRINITRATE	8 (3.3%)	15 (3.1%)	23 (3.2%)
ACETYLCYSTEINE	8 (3.3%)	14 (2.9%)	22 (3.0%)
FUROSEMIDE	8 (3.3%)	14 (2.9%)	22 (3.0%)
ENALAPRIL MALEATE	7 (2.9%)	14 (2.9%)	21 (2.9%)
SIMVASTATIN	9 (3.7%)	10 (2.1%)	19 (2.6%)
CAPTOPRIL	8 (3.3%)	10 (2.1%)	18 (2.5%)
GLIBENCLAMIDE	5 (2.1%)	13 (2.7%)	18 (2.5%)
RANITIDINE HYDROCHLORIDE	3 (1.2%)	15 (3.1%)	18 (2.5%)
CODEINE PHOSPHATE	4 (1.6%)	13 (2.7%)	17 (2.4%)
DEXTROPROPOXYPHENE HYDROCHLORIDE	7 (2.9%)	9 (1.9%)	16 (2.2%)
DILTIAZEM HYDROCHLORIDE	3 (1.2%)	12 (2.5%)	15 (2.1%)
SALBUTAMOL SULFATE	4 (1.6%)	11 (2.3%)	15 (2.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. PRIOR MEDICATIONS DEFINED AS ANY MEDICATION RECEIVED PRIOR TO ENTRY INTO STUDY 040
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL COLUMN

TABLE 13.10A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
ALMAGATE	4 (1.6%)	10 (2.1%)	14 (1.9%)
CALCIUM SACCHARATE	4 (1.6%)	10 (2.1%)	14 (1.9%)
VERAPAMIL HYDROCHLORIDE	5 (2.1%)	9 (1.9%)	14 (1.9%)
DIGOXIN	6 (2.5%)	7 (1.5%)	13 (1.8%)
ISOSORBIDE MONONITRATE	4 (1.6%)	8 (1.7%)	12 (1.7%)
AMLODIPINE BESYLATE	3 (1.2%)	8 (1.7%)	11 (1.5%)
BROMAZEPAM	4 (1.6%)	7 (1.5%)	11 (1.5%)
FENOFIBRATE	5 (2.1%)	6 (1.3%)	11 (1.5%)
METFORMIN HYDROCHLORIDE	5 (2.1%)	6 (1.3%)	11 (1.5%)
MOLSIDOMINE	4 (1.6%)	7 (1.5%)	11 (1.5%)
AMIODARONE HYDROCHLORIDE	4 (1.6%)	6 (1.3%)	10 (1.4%)
ENALAPRIL	2 (0.8%)	8 (1.7%)	10 (1.4%)
LORAZEPAM	5 (2.1%)	5 (1.0%)	10 (1.4%)
SODIUM BICARBONATE	4 (1.6%)	6 (1.3%)	10 (1.4%)
ALUMINIUM HYDROXIDE	5 (2.1%)	4 (0.8%)	9 (1.2%)
MAGNESIUM TRISILICATE	5 (2.1%)	4 (0.8%)	9 (1.2%)
TRIAMTERENE	6 (2.5%)	3 (0.6%)	9 (1.2%)
ACETYLSALICYLATE LYSINE	2 (0.8%)	6 (1.3%)	8 (1.1%)
ALGINIC ACID	4 (1.6%)	4 (0.8%)	8 (1.1%)
AMLODIPINE	4 (1.6%)	4 (0.8%)	8 (1.1%)
DICLOFENAC SODIUM	4 (1.6%)	4 (0.8%)	8 (1.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. PRIOR MEDICATIONS DEFINED AS ANY MEDICATION RECEIVED PRIOR TO ENTRY INTO STUDY 040
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL COLUMN

TABLE 13.10A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
-----	-----	-----	-----
ESTRADIOL	2 (0.8%)	6 (1.3%)	8 (1.1%)
LISINOPRIL	4 (1.6%)	4 (0.8%)	8 (1.1%)
ZOPICLONE	1 (0.4%)	7 (1.5%)	8 (1.1%)
AMBROXOL HYDROCHLORIDE	4 (1.6%)	3 (0.6%)	7 (1.0%)
AMILORIDE HYDROCHLORIDE	3 (1.2%)	4 (0.8%)	7 (1.0%)
ATORVASTATIN	2 (0.8%)	5 (1.0%)	7 (1.0%)
BENDROFLUMETHIAZIDE	3 (1.2%)	4 (0.8%)	7 (1.0%)
IBUPROFEN	1 (0.4%)	6 (1.3%)	7 (1.0%)
IRBESARTAN	3 (1.2%)	4 (0.8%)	7 (1.0%)
LEVOTHYROXINE SODIUM	2 (0.8%)	5 (1.0%)	7 (1.0%)
PIROXICAM	2 (0.8%)	5 (1.0%)	7 (1.0%)
RANITIDINE	5 (2.1%)	2 (0.4%)	7 (1.0%)
SORBITOL	2 (0.8%)	5 (1.0%)	7 (1.0%)
ALGIN	3 (1.2%)	3 (0.6%)	6 (0.8%)
BISOPROLOL	1 (0.4%)	5 (1.0%)	6 (0.8%)
BUFLOMEDIL HYDROCHLORIDE	2 (0.8%)	4 (0.8%)	6 (0.8%)
DIAZEPAM	2 (0.8%)	4 (0.8%)	6 (0.8%)
FELODIPINE	2 (0.8%)	4 (0.8%)	6 (0.8%)
FLUOXETINE	0 .	6 (1.3%)	6 (0.8%)
GLICLAZIDE	2 (0.8%)	4 (0.8%)	6 (0.8%)
GLIMEPIRIDE	1 (0.4%)	5 (1.0%)	6 (0.8%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
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TABLE 13.10A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
INDAPAMIDE	1 (0.4%)	5 (1.0%)	6 (0.8%)
ISOSORBIDE DINITRATE	0 .	6 (1.3%)	6 (0.8%)
LORATADINE	1 (0.4%)	5 (1.0%)	6 (0.8%)
LOSARTAN POTASSIUM	0 .	6 (1.3%)	6 (0.8%)
METOPROLOL SUCCINATE	0 .	6 (1.3%)	6 (0.8%)
OXITROPIUM BROMIDE	3 (1.2%)	3 (0.6%)	6 (0.8%)
PERINDOPRIL	2 (0.8%)	4 (0.8%)	6 (0.8%)
RAMIPRIL	1 (0.4%)	5 (1.0%)	6 (0.8%)
SPIRONOLACTONE	1 (0.4%)	5 (1.0%)	6 (0.8%)
ATORVASTATIN CALCIUM	5 (2.1%)	0 .	5 (0.7%)
CAFFEINE	1 (0.4%)	4 (0.8%)	5 (0.7%)
CISAPRIDE	0 .	5 (1.0%)	5 (0.7%)
LANSOPRAZOLE	1 (0.4%)	4 (0.8%)	5 (0.7%)
NITRENDIPINE	2 (0.8%)	3 (0.6%)	5 (0.7%)
NORETHISTERONE ACETATE	1 (0.4%)	4 (0.8%)	5 (0.7%)
POTASSIUM CHLORIDE	2 (0.8%)	3 (0.6%)	5 (0.7%)
PRAVASTATIN	1 (0.4%)	4 (0.8%)	5 (0.7%)
ALPRAZOLAM	1 (0.4%)	3 (0.6%)	4 (0.6%)
AMITRIPTYLINE HYDROCHLORIDE	1 (0.4%)	3 (0.6%)	4 (0.6%)
ATENOLOL	2 (0.8%)	2 (0.4%)	4 (0.6%)
CALCIUM CARBONATE	4 (1.6%)	0 .	4 (0.6%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
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TABLE 13.10A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
CARBAMAZEPINE	1 (0.4%)	3 (0.6%)	4 (0.6%)
CARBOCISTEINE	0 .	4 (0.8%)	4 (0.6%)
DIHYDROCODEINE BITARTRATE	3 (1.2%)	1 (0.2%)	4 (0.6%)
DILTIAZEM	2 (0.8%)	2 (0.4%)	4 (0.6%)
DIPOTASSIUM CLORAZEPATE	1 (0.4%)	3 (0.6%)	4 (0.6%)
DOXAZOSIN	3 (1.2%)	1 (0.2%)	4 (0.6%)
ESTROGENS CONJUGATED	1 (0.4%)	3 (0.6%)	4 (0.6%)
FUROSEMIDE XANTINOL	3 (1.2%)	1 (0.2%)	4 (0.6%)
NAFTIDROFURYL OXALATE	0 .	4 (0.8%)	4 (0.6%)
NIMODIPINE	1 (0.4%)	3 (0.6%)	4 (0.6%)
PHENOBARBITAL	1 (0.4%)	3 (0.6%)	4 (0.6%)
RILMENIDINE PHOSPHATE	2 (0.8%)	2 (0.4%)	4 (0.6%)
TRIAMCINOLONE ACETONIDE	1 (0.4%)	3 (0.6%)	4 (0.6%)
TRIMETAZIDINE DIHYDROCHLORIDE	1 (0.4%)	3 (0.6%)	4 (0.6%)
VALSARTAN	2 (0.8%)	2 (0.4%)	4 (0.6%)
ZOLPIDEM HEMITARTRATE	3 (1.2%)	1 (0.2%)	4 (0.6%)
ACENOCOUMAROL	0 .	3 (0.6%)	3 (0.4%)
ACETYLDIGOXIN	3 (1.2%)	0 .	3 (0.4%)
ALFUZOSIN HYDROCHLORIDE	1 (0.4%)	2 (0.4%)	3 (0.4%)
ALMITRINE DIMESILATE	1 (0.4%)	2 (0.4%)	3 (0.4%)
BETAMETHASONE DIPROPIONATE	1 (0.4%)	2 (0.4%)	3 (0.4%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
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TABLE 13.10A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
-----	-----	-----	-----
BEZAFIBRATE	2 (0.8%)	1 (0.2%)	3 (0.4%)
BUMETANIDE	0 .	3 (0.6%)	3 (0.4%)
CARBASALATE CALCIUM	1 (0.4%)	2 (0.4%)	3 (0.4%)
CELIPROLOL HYDROCHLORIDE	0 .	3 (0.6%)	3 (0.4%)
CITALOPRAM	1 (0.4%)	2 (0.4%)	3 (0.4%)
CLARITHROMYCIN	0 .	3 (0.6%)	3 (0.4%)
CLOPIDOGREL	0 .	3 (0.6%)	3 (0.4%)
CLOTRIMAZOLE	1 (0.4%)	2 (0.4%)	3 (0.4%)
CYANOCOBALAMIN	0 .	3 (0.6%)	3 (0.4%)
DORZOLAMIDE HYDROCHLORIDE	0 .	3 (0.6%)	3 (0.4%)
FAMOTIDINE	0 .	3 (0.6%)	3 (0.4%)
FLUNISOLIDE	0 .	3 (0.6%)	3 (0.4%)
FORMOTEROL	0 .	3 (0.6%)	3 (0.4%)
FOSINOPRIL	3 (1.2%)	0 .	3 (0.4%)
GLUTAMIC ACID	1 (0.4%)	2 (0.4%)	3 (0.4%)
HYDROCORTISONE	1 (0.4%)	2 (0.4%)	3 (0.4%)
INSULIN INJECTION, ISOPHANE	0 .	3 (0.6%)	3 (0.4%)
LACTULOSE	2 (0.8%)	1 (0.2%)	3 (0.4%)
LEVONORGESTREL	0 .	3 (0.6%)	3 (0.4%)
MAGNESIUM GLUTAMATE	3 (1.2%)	0 .	3 (0.4%)
MAGNESIUM OXIDE	0 .	3 (0.6%)	3 (0.4%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
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TABLE 13.10A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
METFORMIN	0 .	3 (0.6%)	3 (0.4%)
METOPROLOL	1 (0.4%)	2 (0.4%)	3 (0.4%)
NEOMYCIN SULFATE	0 .	3 (0.6%)	3 (0.4%)
NITRAZEPAM	1 (0.4%)	2 (0.4%)	3 (0.4%)
PENTOXIFYLLINE	0 .	3 (0.6%)	3 (0.4%)
PHENPROCUMON	1 (0.4%)	2 (0.4%)	3 (0.4%)
PHOLCODINE	1 (0.4%)	2 (0.4%)	3 (0.4%)
POTASSIUM ASCORBATE	1 (0.4%)	2 (0.4%)	3 (0.4%)
PRAVASTATIN SODIUM	2 (0.8%)	1 (0.2%)	3 (0.4%)
PYGEUM AFRICANUM	1 (0.4%)	2 (0.4%)	3 (0.4%)
QUININE SULFATE	1 (0.4%)	2 (0.4%)	3 (0.4%)
RAUBASINE	0 .	3 (0.6%)	3 (0.4%)
SILDENAFIL CITRATE	0 .	3 (0.6%)	3 (0.4%)
TAMSULOSIN HYDROCHLORIDE	1 (0.4%)	2 (0.4%)	3 (0.4%)
TERAZOSIN HYDROCHLORIDE	0 .	3 (0.6%)	3 (0.4%)
TOCOPHEROL	2 (0.8%)	1 (0.2%)	3 (0.4%)
TORASEMID	2 (0.8%)	1 (0.2%)	3 (0.4%)
TRANDOLAPRILAT	2 (0.8%)	1 (0.2%)	3 (0.4%)
TRIFLUSAL	1 (0.4%)	2 (0.4%)	3 (0.4%)
VENLAFAXINE	1 (0.4%)	2 (0.4%)	3 (0.4%)
VERAPAMIL	1 (0.4%)	2 (0.4%)	3 (0.4%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
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TABLE 13.10A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
ACARBOSE	1 (0.4%)	1 (0.2%)	2 (0.3%)
ACECLOFENAC	1 (0.4%)	1 (0.2%)	2 (0.3%)
ALANINE	1 (0.4%)	1 (0.2%)	2 (0.3%)
ALFUZOSIN	1 (0.4%)	1 (0.2%)	2 (0.3%)
ALMASILATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
ALTIZIDE	0 .	2 (0.4%)	2 (0.3%)
ALUMINIUM GLYCINATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
AMINOACETIC ACID	1 (0.4%)	1 (0.2%)	2 (0.3%)
ASCORBIC ACID	1 (0.4%)	1 (0.2%)	2 (0.3%)
BENZALKONIUM CHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
BETAHISTINE HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
BETAMETHASONE VALERATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
BETAXOLOL HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)
BISOPROLOL FUMARATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
BRIMONIDINE TARTRATE	0 .	2 (0.4%)	2 (0.3%)
BROMELAINS	0 .	2 (0.4%)	2 (0.3%)
BUDESONIDE	0 .	2 (0.4%)	2 (0.3%)
CALCIUM	0 .	2 (0.4%)	2 (0.3%)
CANDESARTAN CILEXETIL	1 (0.4%)	1 (0.2%)	2 (0.3%)
CERIVASTATIN	1 (0.4%)	1 (0.2%)	2 (0.3%)
CETIRIZINE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
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TABLE 13.10A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
CHLORPHENAMINE MALEATE	0 .	2 (0.4%)	2 (0.3%)
CHLORTALIDONE	1 (0.4%)	1 (0.2%)	2 (0.3%)
CIBENZOLINE SUCCINATE	0 .	2 (0.4%)	2 (0.3%)
CLOMIPRAMINE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)
CLONIDINE HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
COCARBOXYLASE	0 .	2 (0.4%)	2 (0.3%)
COLECALCIFEROL	1 (0.4%)	1 (0.2%)	2 (0.3%)
CRATAEGUS	0 .	2 (0.4%)	2 (0.3%)
DESIPRAMINE HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
DICLOFENAC	2 (0.8%)	0 .	2 (0.3%)
DIMETICONE	1 (0.4%)	1 (0.2%)	2 (0.3%)
DOMPERIDONE	0 .	2 (0.4%)	2 (0.3%)
DOSULEPIN	0 .	2 (0.4%)	2 (0.3%)
DOXAZOSIN MESYLATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
DOXEPIN	1 (0.4%)	1 (0.2%)	2 (0.3%)
DOXEPIN HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
EPHEDRINE HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
ESTRADIOL VALERATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
ESTRIOL	0 .	2 (0.4%)	2 (0.3%)
ETHINYLESTRADIOL	0 .	2 (0.4%)	2 (0.3%)
FENOTEROL HYDROBROMIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)

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TABLE 13.10A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
FENOXAZOLINE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)
FERROUS SULFATE	0 .	2 (0.4%)	2 (0.3%)
FEXOFENADINE HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
FLECAINIDE ACETATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
FLUINDIONE	1 (0.4%)	1 (0.2%)	2 (0.3%)
FLUVASTATIN SODIUM	1 (0.4%)	1 (0.2%)	2 (0.3%)
FOLIC ACID	0 .	2 (0.4%)	2 (0.3%)
GEMFIBROZIL	0 .	2 (0.4%)	2 (0.3%)
GINKGO TREE LEAVES EXTRACT	1 (0.4%)	1 (0.2%)	2 (0.3%)
HALAZEPAM	0 .	2 (0.4%)	2 (0.3%)
HEPTAMINOL HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
HYDROXYZINE HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
INSULIN HUMAN	0 .	2 (0.4%)	2 (0.3%)
LACIDIPINE	0 .	2 (0.4%)	2 (0.3%)
LATANOPROST	0 .	2 (0.4%)	2 (0.3%)
MEDAZEPAM	0 .	2 (0.4%)	2 (0.3%)
MELOXICAM	1 (0.4%)	1 (0.2%)	2 (0.3%)
MEPROBAMATE	0 .	2 (0.4%)	2 (0.3%)
METOPROLOL TARTRATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
MISOPROSTOL	2 (0.8%)	0 .	2 (0.3%)
MORPHINE SULFATE	1 (0.4%)	1 (0.2%)	2 (0.3%)

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TABLE 13.10A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
MYRTILLUS	1 (0.4%)	1 (0.2%)	2 (0.3%)
NICARDIPINE HYDROCHLORIDE	2 (0.8%)	0 .	2 (0.3%)
NYSTATIN	0 .	2 (0.4%)	2 (0.3%)
PANCREATIN	1 (0.4%)	1 (0.2%)	2 (0.3%)
PAROXETINE	1 (0.4%)	1 (0.2%)	2 (0.3%)
PIRETANIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
PRAZOSIN	1 (0.4%)	1 (0.2%)	2 (0.3%)
PRAZOSIN HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
PROCHLORPERAZINE	1 (0.4%)	1 (0.2%)	2 (0.3%)
PROPRANOLOL	1 (0.4%)	1 (0.2%)	2 (0.3%)
PRUNUS AFRICANA	1 (0.4%)	1 (0.2%)	2 (0.3%)
PYRIDOXINE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)
QUINAPRIL HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
QUININE	1 (0.4%)	1 (0.2%)	2 (0.3%)
SABAL EXTRACT	0 .	2 (0.4%)	2 (0.3%)
SERENOA REPENS	2 (0.8%)	0 .	2 (0.3%)
SOTALOL HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)
SULPIRIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
TETRAZEPAM	0 .	2 (0.4%)	2 (0.3%)
THYROXINE	0 .	2 (0.4%)	2 (0.3%)
TIMOLOL	2 (0.8%)	0 .	2 (0.3%)

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SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
TIMOLOL MALEATE	0 .	2 (0.4%)	2 (0.3%)
TOLTERODINE	2 (0.8%)	0 .	2 (0.3%)
TROSPIMUM CHLORIDE	2 (0.8%)	0 .	2 (0.3%)
URTICA EXTRACT	0 .	2 (0.4%)	2 (0.3%)
VALERIAN ROOT	1 (0.4%)	1 (0.2%)	2 (0.3%)
VENLAFAXINE HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
WARFARIN	1 (0.4%)	1 (0.2%)	2 (0.3%)
WARFARIN SODIUM	1 (0.4%)	1 (0.2%)	2 (0.3%)
ACETAZOLAMIDE	0 .	1 (0.2%)	1 (0.1%)
ACEXAMATE ZINC	0 .	1 (0.2%)	1 (0.1%)
ADENOSINE TRIPHOSPHATE	0 .	1 (0.2%)	1 (0.1%)
ALENDRONATE	0 .	1 (0.2%)	1 (0.1%)
ALFACALCIDOL	1 (0.4%)	0 .	1 (0.1%)
ALLERGENIC EXTRACT, NOS	0 .	1 (0.2%)	1 (0.1%)
AMINEPTINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
AMINOHYDROXYPROPYLIDENEDIPHOSPHONATE DISODIUM	1 (0.4%)	0 .	1 (0.1%)
AMINOSALICYLIC ACID	0 .	1 (0.2%)	1 (0.1%)
AMIODARONE	0 .	1 (0.2%)	1 (0.1%)
AMISULPRIDE	1 (0.4%)	0 .	1 (0.1%)
AMOXICILLIN TRIHYDRATE	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. PRIOR MEDICATIONS DEFINED AS ANY MEDICATION RECEIVED PRIOR TO ENTRY INTO STUDY 040
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL COLUMN

TABLE 13.10A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
ARGININE ASPARTATE	0 .	1 (0.2%)	1 (0.1%)
ASPARTATE MAGNESIUM	0 .	1 (0.2%)	1 (0.1%)
ASPARTATE POTASSIUM	0 .	1 (0.2%)	1 (0.1%)
ATROPINE BORATE	0 .	1 (0.2%)	1 (0.1%)
AZITHROMYCIN	0 .	1 (0.2%)	1 (0.1%)
BECLOMETASONE DIPROPIONATE	0 .	1 (0.2%)	1 (0.1%)
BELLADONNA EXTRACT	0 .	1 (0.2%)	1 (0.1%)
BEMETIZIDE	0 .	1 (0.2%)	1 (0.1%)
BENFOTIAMINE	0 .	1 (0.2%)	1 (0.1%)
BETACAROTENE	0 .	1 (0.2%)	1 (0.1%)
BETAXOLOL	0 .	1 (0.2%)	1 (0.1%)
BIPERIDEN HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
BUTALBITAL	0 .	1 (0.2%)	1 (0.1%)
CALCIUM GLUBIONATE	1 (0.4%)	0 .	1 (0.1%)
CAPSAICIN	0 .	1 (0.2%)	1 (0.1%)
CARBACHOL	0 .	1 (0.2%)	1 (0.1%)
CARBIMAZOLE	0 .	1 (0.2%)	1 (0.1%)
CARBOMER	0 .	1 (0.2%)	1 (0.1%)
CARVEDILOL	1 (0.4%)	0 .	1 (0.1%)
CEFAZOLIN SODIUM	0 .	1 (0.2%)	1 (0.1%)
CELECOXIB	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. PRIOR MEDICATIONS DEFINED AS ANY MEDICATION RECEIVED PRIOR TO ENTRY INTO STUDY 040
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL COLUMN

TABLE 13.10A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
CHLORDIAZEPOXIDE	1 (0.4%)	0 .	1 (0.1%)
CHLORDIAZEPOXIDE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
CHLORMADINONE ACETATE	0 .	1 (0.2%)	1 (0.1%)
CHLORMEZANONE	0 .	1 (0.2%)	1 (0.1%)
CHLORPROPAMIDE	0 .	1 (0.2%)	1 (0.1%)
CIMETIDINE	0 .	1 (0.2%)	1 (0.1%)
CINCHOCAINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
CIPROFIBRATE	0 .	1 (0.2%)	1 (0.1%)
CIPROFLOXACIN	1 (0.4%)	0 .	1 (0.1%)
CLAVULANIC ACID	0 .	1 (0.2%)	1 (0.1%)
CLEBOPRIDE	1 (0.4%)	0 .	1 (0.1%)
CLEMASTINE	0 .	1 (0.2%)	1 (0.1%)
CLOBETASOL PROPIONATE	1 (0.4%)	0 .	1 (0.1%)
CLOBETASONE BUTYRATE	0 .	1 (0.2%)	1 (0.1%)
CODEINE	1 (0.4%)	0 .	1 (0.1%)
CROMOGLICATE SODIUM	0 .	1 (0.2%)	1 (0.1%)
CROTAMITON	0 .	1 (0.2%)	1 (0.1%)
CUCURBITA PEPO	0 .	1 (0.2%)	1 (0.1%)
CYAMEMAZINE	0 .	1 (0.2%)	1 (0.1%)
DANTRON	0 .	1 (0.2%)	1 (0.1%)
DEANOL PIDOLATE	1 (0.4%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. PRIOR MEDICATIONS DEFINED AS ANY MEDICATION RECEIVED PRIOR TO ENTRY INTO STUDY 040
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL COLUMN

TABLE 13.10A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
DESOXIMETASONE	1 (0.4%)	0 .	1 (0.1%)
DEXAMETHASONE	0 .	1 (0.2%)	1 (0.1%)
DEXCHLORPHENIRAMINE MALEATE	0 .	1 (0.2%)	1 (0.1%)
DIASTASE	0 .	1 (0.2%)	1 (0.1%)
DICLOFENAC DIETHYLAMINE	1 (0.4%)	0 .	1 (0.1%)
DICYCLOVERINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
DIENESTROL	1 (0.4%)	0 .	1 (0.1%)
DIETHYLAMINE SALICYLATE	0 .	1 (0.2%)	1 (0.1%)
DIFLUCORTOLONE VALERATE	0 .	1 (0.2%)	1 (0.1%)
DIGITOXIN	0 .	1 (0.2%)	1 (0.1%)
DIHYDROERGOCRISTINE MESILATE	0 .	1 (0.2%)	1 (0.1%)
DIHYDROERGOCRYPTINE MESILATE	1 (0.4%)	0 .	1 (0.1%)
DIHYDROERGOTAMINE MESILATE	0 .	1 (0.2%)	1 (0.1%)
DIMETICONE, ACTIVATED	1 (0.4%)	0 .	1 (0.1%)
DISOPYRAMIDE	1 (0.4%)	0 .	1 (0.1%)
DISOPYRAMIDE PHOSPHATE	0 .	1 (0.2%)	1 (0.1%)
DITAZOLE	0 .	1 (0.2%)	1 (0.1%)
DOCUSATE SODIUM	0 .	1 (0.2%)	1 (0.1%)
DOXYLAMINE SUCCINATE	0 .	1 (0.2%)	1 (0.1%)
EPROSARTAN	0 .	1 (0.2%)	1 (0.1%)
ERYTHROMYCIN	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. PRIOR MEDICATIONS DEFINED AS ANY MEDICATION RECEIVED PRIOR TO ENTRY INTO STUDY 040
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL COLUMN

SB 207499

TABLE 13.10A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
-----	-----	-----	-----
ESCULIN	0 .	1 (0.2%)	1 (0.1%)
ESTROGEN NOS	0 .	1 (0.2%)	1 (0.1%)
ETHENZAMIDE	0 .	1 (0.2%)	1 (0.1%)
ETIDRONATE DISODIUM	1 (0.4%)	0 .	1 (0.1%)
ETILEFRINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
FENDILINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
FINASTERIDE	1 (0.4%)	0 .	1 (0.1%)
FLECAINIDE	0 .	1 (0.2%)	1 (0.1%)
FLUNARIZINE DIHYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
FLUOCINOLONE ACETONIDE	0 .	1 (0.2%)	1 (0.1%)
FLUOXETINE HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)
FLURAZEPAM HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)
FLUTICASONE	0 .	1 (0.2%)	1 (0.1%)
FLUTICASONE PROPIONATE	0 .	1 (0.2%)	1 (0.1%)
FORMOTEROL FUMARATE	1 (0.4%)	0 .	1 (0.1%)
FRAMYCETIN SULFATE	0 .	1 (0.2%)	1 (0.1%)
FUSIDATE SODIUM	1 (0.4%)	0 .	1 (0.1%)
GALLOPAMIL HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)
GENTAMICIN SULFATE	0 .	1 (0.2%)	1 (0.1%)
GINSENG	0 .	1 (0.2%)	1 (0.1%)
GLIPIZIDE	1 (0.4%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. PRIOR MEDICATIONS DEFINED AS ANY MEDICATION RECEIVED PRIOR TO ENTRY INTO STUDY 040
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL COLUMN

TABLE 13.10A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
GLUCOSAMINE	0 .	1 (0.2%)	1 (0.1%)
GLUTATHIONE	0 .	1 (0.2%)	1 (0.1%)
GLYCOL SALICYLATE	0 .	1 (0.2%)	1 (0.1%)
GOSERELIN	0 .	1 (0.2%)	1 (0.1%)
GRAMICIDIN	0 .	1 (0.2%)	1 (0.1%)
HALOPERIDOL	0 .	1 (0.2%)	1 (0.1%)
HELICIDINE	0 .	1 (0.2%)	1 (0.1%)
HEMATOPORPHYRIN	0 .	1 (0.2%)	1 (0.1%)
HIDROSMIN	0 .	1 (0.2%)	1 (0.1%)
HISTAMINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
HYDROCORTISONE ACETATE	0 .	1 (0.2%)	1 (0.1%)
HYDROXOCOBALAMIN	0 .	1 (0.2%)	1 (0.1%)
HYDROXYCHLOROQUINE SULFATE	0 .	1 (0.2%)	1 (0.1%)
HYDROXYETHYLCELLULOSE	1 (0.4%)	0 .	1 (0.1%)
HYPERICUM EXTRACT	0 .	1 (0.2%)	1 (0.1%)
INDOMETACIN	0 .	1 (0.2%)	1 (0.1%)
INOSINE	0 .	1 (0.2%)	1 (0.1%)
INSULIN	0 .	1 (0.2%)	1 (0.1%)
INSULIN HUMAN INJECTION, ISOPHANE	0 .	1 (0.2%)	1 (0.1%)
IPRATROPIUM HYDROXIDE	0 .	1 (0.2%)	1 (0.1%)
ISPAGHULA	1 (0.4%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. PRIOR MEDICATIONS DEFINED AS ANY MEDICATION RECEIVED PRIOR TO ENTRY INTO STUDY 040
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL COLUMN

TABLE 13.10A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
ISPAGHULA HUSKS	0 .	1 (0.2%)	1 (0.1%)
KETAZOLAM	0 .	1 (0.2%)	1 (0.1%)
KETOPROFEN	1 (0.4%)	0 .	1 (0.1%)
KETOROLAC TROMETHAMINE	1 (0.4%)	0 .	1 (0.1%)
KETOTIFEN FUMARATE	1 (0.4%)	0 .	1 (0.1%)
LACTITOL	0 .	1 (0.2%)	1 (0.1%)
LANOLIN	0 .	1 (0.2%)	1 (0.1%)
LERCANIDIPINE	1 (0.4%)	0 .	1 (0.1%)
LEVOBUNOLOL HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
LEVOMEPRMAZINE MALEATE	1 (0.4%)	0 .	1 (0.1%)
LIPOPHILER EXTRACT	0 .	1 (0.2%)	1 (0.1%)
LIVER EXTRACTS	0 .	1 (0.2%)	1 (0.1%)
LOPRAZOLAM MESILATE	1 (0.4%)	0 .	1 (0.1%)
LORMETAZEPAM	0 .	1 (0.2%)	1 (0.1%)
LOSARTAN	1 (0.4%)	0 .	1 (0.1%)
MAGNESIUM ASCORBATE	0 .	1 (0.2%)	1 (0.1%)
MAGNESIUM CARBONATE	0 .	1 (0.2%)	1 (0.1%)
MAGNESIUM HYDROXIDE	0 .	1 (0.2%)	1 (0.1%)
MAGNESIUM NOS	1 (0.4%)	0 .	1 (0.1%)
MAGNESIUM SALT	0 .	1 (0.2%)	1 (0.1%)
MAPROTILINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. PRIOR MEDICATIONS DEFINED AS ANY MEDICATION RECEIVED PRIOR TO ENTRY INTO STUDY 040
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL COLUMN

TABLE 13.10A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
MEBEVERINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
MEDROGESTONE	1 (0.4%)	0 .	1 (0.1%)
METAMIZOLE	1 (0.4%)	0 .	1 (0.1%)
METFORMIN EMBONATE	0 .	1 (0.2%)	1 (0.1%)
METHENAMINE HIPPURATE	0 .	1 (0.2%)	1 (0.1%)
METHOTREXATE	1 (0.4%)	0 .	1 (0.1%)
METHYCLOTHIAZIDE	1 (0.4%)	0 .	1 (0.1%)
METHYL NICOTINATE	0 .	1 (0.2%)	1 (0.1%)
METHYLDOPA	0 .	1 (0.2%)	1 (0.1%)
METHYLPREDNISOLONE	0 .	1 (0.2%)	1 (0.1%)
METILDIGOXIN	0 .	1 (0.2%)	1 (0.1%)
MIANSERIN	0 .	1 (0.2%)	1 (0.1%)
MIANSERIN HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
MICONAZOLE NITRATE	0 .	1 (0.2%)	1 (0.1%)
MINERAL OIL, LIGHT	0 .	1 (0.2%)	1 (0.1%)
MINERALS NOS	0 .	1 (0.2%)	1 (0.1%)
MISTLETOE EXTRACT	0 .	1 (0.2%)	1 (0.1%)
MOCLOBEMIDE	1 (0.4%)	0 .	1 (0.1%)
NABUMETONE	0 .	1 (0.2%)	1 (0.1%)
NAPROXEN	0 .	1 (0.2%)	1 (0.1%)
NAPROXEN SODIUM	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. PRIOR MEDICATIONS DEFINED AS ANY MEDICATION RECEIVED PRIOR TO ENTRY INTO STUDY 040
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL COLUMN

SB 207499

TABLE 13.10A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
NEOMYCIN	1 (0.4%)	0 .	1 (0.1%)
NIAOULI OIL	1 (0.4%)	0 .	1 (0.1%)
NICERGOLINE	0 .	1 (0.2%)	1 (0.1%)
NICORANDIL	0 .	1 (0.2%)	1 (0.1%)
NICOTINE RESIN	1 (0.4%)	0 .	1 (0.1%)
NIZATIDINE	0 .	1 (0.2%)	1 (0.1%)
NORETHISTERONE	1 (0.4%)	0 .	1 (0.1%)
NOSCAPINE	0 .	1 (0.2%)	1 (0.1%)
NUCLEOTIDES NOS	0 .	1 (0.2%)	1 (0.1%)
NUTRITIONAL SUPPLEMENT NOS	0 .	1 (0.2%)	1 (0.1%)
OMEPRAZOLE SODIUM	0 .	1 (0.2%)	1 (0.1%)
ORANGE COLOURING	0 .	1 (0.2%)	1 (0.1%)
ORANGE ESSENCE	0 .	1 (0.2%)	1 (0.1%)
OROTIC ACID	0 .	1 (0.2%)	1 (0.1%)
OXACEPROL	1 (0.4%)	0 .	1 (0.1%)
OXAZEPAM	0 .	1 (0.2%)	1 (0.1%)
OXETACAINE	0 .	1 (0.2%)	1 (0.1%)
OXYFEDRINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
OXYTETRACYCLINE	1 (0.4%)	0 .	1 (0.1%)
OXYTETRACYCLINE CALCIUM	0 .	1 (0.2%)	1 (0.1%)
PANTOPRAZOL	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. PRIOR MEDICATIONS DEFINED AS ANY MEDICATION RECEIVED PRIOR TO ENTRY INTO STUDY 040
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL COLUMN

TABLE 13.10A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
PARAFFIN, SOFT	0 .	1 (0.2%)	1 (0.1%)
PARAHYDROXYCINNAMIC ACID	0 .	1 (0.2%)	1 (0.1%)
PENTOSAN POLYSULFATE SODIUM	0 .	1 (0.2%)	1 (0.1%)
PEPSIN	0 .	1 (0.2%)	1 (0.1%)
PHENOBARBITAL CALCIUM	0 .	1 (0.2%)	1 (0.1%)
PHENYLEPHRINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
PHENYTOIN	1 (0.4%)	0 .	1 (0.1%)
PILOCARPINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
PIRIBEDIL	1 (0.4%)	0 .	1 (0.1%)
PIROXICAM BETA CYCLODEXTRIN	0 .	1 (0.2%)	1 (0.1%)
POLYMYXIN B SULFATE	0 .	1 (0.2%)	1 (0.1%)
POPULUS EXTRACT	0 .	1 (0.2%)	1 (0.1%)
POPULUS TREMULA	0 .	1 (0.2%)	1 (0.1%)
PREDNISONE	1 (0.4%)	0 .	1 (0.1%)
PROGESTERONE	0 .	1 (0.2%)	1 (0.1%)
PROPAFENONE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
PROPANTHELINE BROMIDE	0 .	1 (0.2%)	1 (0.1%)
PROPYPHENAZONE	0 .	1 (0.2%)	1 (0.1%)
PYRIDOXINE	0 .	1 (0.2%)	1 (0.1%)
QUINAPRIL	1 (0.4%)	0 .	1 (0.1%)
QUININE BENZOATE	1 (0.4%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. PRIOR MEDICATIONS DEFINED AS ANY MEDICATION RECEIVED PRIOR TO ENTRY INTO STUDY 040
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL COLUMN

SB 207499

TABLE 13.10A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
RAUWOLFIA	0 .	1 (0.2%)	1 (0.1%)
RESCINNAMINE	1 (0.4%)	0 .	1 (0.1%)
RESERPINE	0 .	1 (0.2%)	1 (0.1%)
RUSCUS ACULEATUS RHIZOME	1 (0.4%)	0 .	1 (0.1%)
RUTOSIDE	0 .	1 (0.2%)	1 (0.1%)
SACCHARIN SODIUM	0 .	1 (0.2%)	1 (0.1%)
SACCHAROSE	0 .	1 (0.2%)	1 (0.1%)
SALICYLAMIDE	0 .	1 (0.2%)	1 (0.1%)
SERTRALINE	0 .	1 (0.2%)	1 (0.1%)
SIBUTRAMINE	0 .	1 (0.2%)	1 (0.1%)
SILICON DIOXIDE, COLLOIDAL	0 .	1 (0.2%)	1 (0.1%)
SITOSTEROLS	1 (0.4%)	0 .	1 (0.1%)
SODIUM AUROTHIOMALATE	1 (0.4%)	0 .	1 (0.1%)
SODIUM CHLORIDE	1 (0.4%)	0 .	1 (0.1%)
SODIUM FLUORIDE	0 .	1 (0.2%)	1 (0.1%)
SODIUM MONOMETHYLTRISILANOL ORTHOHYDROXY-BENZOATE	0 .	1 (0.2%)	1 (0.1%)
SULFASALAZINE	1 (0.4%)	0 .	1 (0.1%)
SUMATRIPTAN	0 .	1 (0.2%)	1 (0.1%)
TAMOXIFEN	1 (0.4%)	0 .	1 (0.1%)
TAXOL	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. PRIOR MEDICATIONS DEFINED AS ANY MEDICATION RECEIVED PRIOR TO ENTRY INTO STUDY 040
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL COLUMN

SB 207499

TABLE 13.10A

SUMMARY OF PRIOR MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
TERBUTALINE SULFATE	0 .	1 (0.2%)	1 (0.1%)
TESTOSTERONE ENANTATE	1 (0.4%)	0 .	1 (0.1%)
THERAPEUTIC RADIATION NOS	0 .	1 (0.2%)	1 (0.1%)
THIAMINE HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)
THIAMINE MONONITRATE	0 .	1 (0.2%)	1 (0.1%)
TICLOPIDINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
TOLBUTAMIDE	0 .	1 (0.2%)	1 (0.1%)
TOLFENAMIC ACID	1 (0.4%)	0 .	1 (0.1%)
TOPICAL STEROID NOS	0 .	1 (0.2%)	1 (0.1%)
TRAMADOL HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
TRAPIDIL	0 .	1 (0.2%)	1 (0.1%)
TRAZODONE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
TRIMIPRAMINE	0 .	1 (0.2%)	1 (0.1%)
TROXERUTIN	0 .	1 (0.2%)	1 (0.1%)
UNDECYLENIC ACID	1 (0.4%)	0 .	1 (0.1%)
VALPROATE SODIUM	0 .	1 (0.2%)	1 (0.1%)
VILOXAZINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
VINCAMINE	0 .	1 (0.2%)	1 (0.1%)
VIRGAUREA HERB	0 .	1 (0.2%)	1 (0.1%)
VITAMINS NOS	0 .	1 (0.2%)	1 (0.1%)
ZOLMITRIPTAN	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING PRIOR MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. PRIOR MEDICATIONS DEFINED AS ANY MEDICATION RECEIVED PRIOR TO ENTRY INTO STUDY 040
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL COLUMN

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)		PRIOR TREATMENT SB 207499 (N=480)		Total (N=723)	
TOTAL	243	(100.0%)	479	(99.8%)	722	(99.9%)
SALBUTAMOL	224	(92.2%)	431	(89.8%)	655	(90.6%)
IPRATROPIUM BROMIDE	114	(46.9%)	223	(46.5%)	337	(46.6%)
PARACETAMOL	80	(32.9%)	169	(35.2%)	249	(34.4%)
AMOXICILLIN TRIHYDRATE	69	(28.4%)	138	(28.8%)	207	(28.6%)
CLAVULANIC ACID	46	(18.9%)	106	(22.1%)	152	(21.0%)
ACETYLCYSTEINE	46	(18.9%)	83	(17.3%)	129	(17.8%)
INFLUENZA VIRUS VACCINE POLYVALENT	47	(19.3%)	76	(15.8%)	123	(17.0%)
ACETYLSALICYLIC ACID	37	(15.2%)	80	(16.7%)	117	(16.2%)
PREDNISOLONE	34	(14.0%)	61	(12.7%)	95	(13.1%)
OMEPRAZOLE	27	(11.1%)	62	(12.9%)	89	(12.3%)
AZITHROMYCIN	34	(14.0%)	50	(10.4%)	84	(11.6%)
PREDNISONE	28	(11.5%)	52	(10.8%)	80	(11.1%)
BUDESONIDE	30	(12.3%)	48	(10.0%)	78	(10.8%)
FLUTICASONE PROPIONATE	24	(9.9%)	53	(11.0%)	77	(10.7%)
FORMOTEROL FUMARATE	25	(10.3%)	48	(10.0%)	73	(10.1%)
METHYLPREDNISOLONE	24	(9.9%)	49	(10.2%)	73	(10.1%)
CODEINE PHOSPHATE	15	(6.2%)	49	(10.2%)	64	(8.9%)
CLARITHROMYCIN	18	(7.4%)	45	(9.4%)	63	(8.7%)
CEFUROXIME AXETIL	20	(8.2%)	42	(8.8%)	62	(8.6%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

SB 207499

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
AMOXICILLIN	18 (7.4%)	42 (8.8%)	60 (8.3%)
IBUPROFEN	19 (7.8%)	38 (7.9%)	57 (7.9%)
LEVOFLOXACIN	20 (8.2%)	33 (6.9%)	53 (7.3%)
DICLOFENAC SODIUM	17 (7.0%)	34 (7.1%)	51 (7.1%)
MOXIFLOXACIN	11 (4.5%)	37 (7.7%)	48 (6.6%)
CARBOCISTEINE	17 (7.0%)	30 (6.3%)	47 (6.5%)
RANITIDINE HYDROCHLORIDE	14 (5.8%)	33 (6.9%)	47 (6.5%)
CIPROFLOXACIN	11 (4.5%)	35 (7.3%)	46 (6.4%)
SALMETEROL HYDROXYNAPHTHOATE	15 (6.2%)	31 (6.5%)	46 (6.4%)
SALMETEROL	15 (6.2%)	30 (6.3%)	45 (6.2%)
FUROSEMIDE	14 (5.8%)	30 (6.3%)	44 (6.1%)
HYDROCHLOROTHIAZIDE	15 (6.2%)	29 (6.0%)	44 (6.1%)
FORMOTEROL	10 (4.1%)	33 (6.9%)	43 (5.9%)
ROXITHROMYCIN	12 (4.9%)	28 (5.8%)	40 (5.5%)
SALMETEROL XINAFOATE	13 (5.3%)	26 (5.4%)	39 (5.4%)
ALLOPURINOL	16 (6.6%)	22 (4.6%)	38 (5.3%)
ASCORBIC ACID	12 (4.9%)	26 (5.4%)	38 (5.3%)
DEFLAZACORT	12 (4.9%)	26 (5.4%)	38 (5.3%)
CEFIXIME	13 (5.3%)	23 (4.8%)	36 (5.0%)
GLYCERYL TRINITRATE	14 (5.8%)	22 (4.6%)	36 (5.0%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
ALMAGATE	14 (5.8%)	21 (4.4%)	35 (4.8%)
CAFFEINE	8 (3.3%)	27 (5.6%)	35 (4.8%)
DEXTROPROPOXYPHENE HYDROCHLORIDE	14 (5.8%)	21 (4.4%)	35 (4.8%)
CALCIUM SACCHARATE	13 (5.3%)	21 (4.4%)	34 (4.7%)
AMBROXOL HYDROCHLORIDE	14 (5.8%)	18 (3.8%)	32 (4.4%)
CIPROFLOXACIN HYDROCHLORIDE	15 (6.2%)	17 (3.5%)	32 (4.4%)
PREDNISOLONE SODIUM SULFOBENZOATE	11 (4.5%)	21 (4.4%)	32 (4.4%)
FLUTICASONE	10 (4.1%)	21 (4.4%)	31 (4.3%)
TRIMETHOPRIM	6 (2.5%)	24 (5.0%)	30 (4.1%)
ENALAPRIL MALEATE	8 (3.3%)	21 (4.4%)	29 (4.0%)
METAMIZOLE	9 (3.7%)	19 (4.0%)	28 (3.9%)
NIFEDIPINE	6 (2.5%)	22 (4.6%)	28 (3.9%)
SODIUM BICARBONATE	8 (3.3%)	20 (4.2%)	28 (3.9%)
RANITIDINE	11 (4.5%)	16 (3.3%)	27 (3.7%)
SALBUTAMOL SULFATE	10 (4.1%)	17 (3.5%)	27 (3.7%)
THEOPHYLLINE	5 (2.1%)	22 (4.6%)	27 (3.7%)
SIMVASTATIN	10 (4.1%)	16 (3.3%)	26 (3.6%)
CAPTOPRIL	9 (3.7%)	16 (3.3%)	25 (3.5%)
CEFTRIAXONE SODIUM	10 (4.1%)	13 (2.7%)	23 (3.2%)
DIGOXIN	9 (3.7%)	14 (2.9%)	23 (3.2%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
LORATADINE	8 (3.3%)	15 (3.1%)	23 (3.2%)
ALUMINIUM HYDROXIDE	8 (3.3%)	14 (2.9%)	22 (3.0%)
BETAMETHASONE SODIUM PHOSPHATE	5 (2.1%)	17 (3.5%)	22 (3.0%)
DILTIAZEM HYDROCHLORIDE	5 (2.1%)	17 (3.5%)	22 (3.0%)
DOXYCYCLINE	5 (2.1%)	17 (3.5%)	22 (3.0%)
ERYTHROMYCIN	3 (1.2%)	19 (4.0%)	22 (3.0%)
LANSOPRAZOLE	7 (2.9%)	15 (3.1%)	22 (3.0%)
BECLOMETASONE DIPROPIONATE	9 (3.7%)	12 (2.5%)	21 (2.9%)
CEFPODOXIME PROXETIL	7 (2.9%)	14 (2.9%)	21 (2.9%)
DIAZEPAM	8 (3.3%)	13 (2.7%)	21 (2.9%)
LORAZEPAM	8 (3.3%)	13 (2.7%)	21 (2.9%)
PHENYLEPHRINE HYDROCHLORIDE	10 (4.1%)	10 (2.1%)	20 (2.8%)
PIROXICAM	5 (2.1%)	15 (3.1%)	20 (2.8%)
POTASSIUM CHLORIDE	6 (2.5%)	14 (2.9%)	20 (2.8%)
SALICYLAMIDE	6 (2.5%)	14 (2.9%)	20 (2.8%)
SODIUM CHLORIDE	11 (4.5%)	9 (1.9%)	20 (2.8%)
VERAPAMIL HYDROCHLORIDE	7 (2.9%)	13 (2.7%)	20 (2.8%)
ENOXAPARIN	5 (2.1%)	14 (2.9%)	19 (2.6%)
FENOTEROL HYDROBROMIDE	4 (1.6%)	15 (3.1%)	19 (2.6%)
GLIBENCLAMIDE	5 (2.1%)	14 (2.9%)	19 (2.6%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
-----	-----	-----	-----
TRIAMCINOLONE ACETONIDE	5 (2.1%)	14 (2.9%)	19 (2.6%)
OFLOXACIN	5 (2.1%)	13 (2.7%)	18 (2.5%)
TRAMADOL HYDROCHLORIDE	4 (1.6%)	14 (2.9%)	18 (2.5%)
AMBROXOL	4 (1.6%)	13 (2.7%)	17 (2.4%)
BROMAZEPAM	8 (3.3%)	9 (1.9%)	17 (2.4%)
DEXAMETHASONE	6 (2.5%)	11 (2.3%)	17 (2.4%)
METHYLPREDNISOLONE SODIUM SUCCINATE	4 (1.6%)	13 (2.7%)	17 (2.4%)
PNEUMOCOCCAL VACCINE	5 (2.1%)	12 (2.5%)	17 (2.4%)
SORBITOL	8 (3.3%)	9 (1.9%)	17 (2.4%)
TERBUTALINE SULFATE	4 (1.6%)	13 (2.7%)	17 (2.4%)
BETAMETHASONE ACETATE	3 (1.2%)	13 (2.7%)	16 (2.2%)
CHLORPHENAMINE MALEATE	5 (2.1%)	11 (2.3%)	16 (2.2%)
HEPARIN-FRACTION, CALCIUM SALT	3 (1.2%)	13 (2.7%)	16 (2.2%)
NYSTATIN	6 (2.5%)	10 (2.1%)	16 (2.2%)
SPIRONOLACTONE	7 (2.9%)	9 (1.9%)	16 (2.2%)
AMIODARONE HYDROCHLORIDE	6 (2.5%)	9 (1.9%)	15 (2.1%)
DICLOFENAC	4 (1.6%)	11 (2.3%)	15 (2.1%)
ISOSORBIDE MONONITRATE	5 (2.1%)	10 (2.1%)	15 (2.1%)
MAGNESIUM TRISILICATE	6 (2.5%)	9 (1.9%)	15 (2.1%)
OXYGEN	6 (2.5%)	9 (1.9%)	15 (2.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
PHOLCODINE	5 (2.1%)	10 (2.1%)	15 (2.1%)
ALGINIC ACID	5 (2.1%)	9 (1.9%)	14 (1.9%)
AMLODIPINE BESYLATE	5 (2.1%)	9 (1.9%)	14 (1.9%)
CIPROFLOXACIN LACTATE	3 (1.2%)	11 (2.3%)	14 (1.9%)
CLAVULANATE POTASSIUM	7 (2.9%)	7 (1.5%)	14 (1.9%)
CODEINE	6 (2.5%)	8 (1.7%)	14 (1.9%)
ENALAPRIL	3 (1.2%)	11 (2.3%)	14 (1.9%)
ISOSORBIDE DINITRATE	4 (1.6%)	10 (2.1%)	14 (1.9%)
LISINOPRIL	5 (2.1%)	9 (1.9%)	14 (1.9%)
METFORMIN HYDROCHLORIDE	6 (2.5%)	8 (1.7%)	14 (1.9%)
NEOMYCIN SULFATE	5 (2.1%)	9 (1.9%)	14 (1.9%)
FENOFIBRATE	5 (2.1%)	8 (1.7%)	13 (1.8%)
FLUOXETINE	2 (0.8%)	11 (2.3%)	13 (1.8%)
HYDROXYZINE HYDROCHLORIDE	5 (2.1%)	8 (1.7%)	13 (1.8%)
IPRATROPIUM HYDROXIDE	6 (2.5%)	7 (1.5%)	13 (1.8%)
LACTULOSE	4 (1.6%)	9 (1.9%)	13 (1.8%)
MENTHOL	3 (1.2%)	10 (2.1%)	13 (1.8%)
MOLSIDOMINE	4 (1.6%)	9 (1.9%)	13 (1.8%)
PRISTINAMYCIN	2 (0.8%)	11 (2.3%)	13 (1.8%)
PROCHLORPERAZINE	5 (2.1%)	8 (1.7%)	13 (1.8%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
THIAMINE HYDROCHLORIDE	7 (2.9%)	6 (1.3%)	13 (1.8%)
ZOPICLONE	2 (0.8%)	11 (2.3%)	13 (1.8%)
ACETYLSALICYLATE LYSINE	3 (1.2%)	9 (1.9%)	12 (1.7%)
ALGIN	4 (1.6%)	8 (1.7%)	12 (1.7%)
BETAMETHASONE VALERATE	3 (1.2%)	9 (1.9%)	12 (1.7%)
CEFACLOX	6 (2.5%)	6 (1.3%)	12 (1.7%)
CLOPIDOGREL	2 (0.8%)	10 (2.1%)	12 (1.7%)
METAMIZOLE SODIUM	0 .	12 (2.5%)	12 (1.7%)
MISOPROSTOL	4 (1.6%)	8 (1.7%)	12 (1.7%)
PREDNISOLONE SODIUM SUCCINATE	2 (0.8%)	10 (2.1%)	12 (1.7%)
PSEUDOEPHEDRINE HYDROCHLORIDE	2 (0.8%)	10 (2.1%)	12 (1.7%)
PYRIDOXINE HYDROCHLORIDE	6 (2.5%)	6 (1.3%)	12 (1.7%)
QUININE SULFATE	4 (1.6%)	8 (1.7%)	12 (1.7%)
SODIUM CITRATE	3 (1.2%)	9 (1.9%)	12 (1.7%)
TAMSULOSIN HYDROCHLORIDE	6 (2.5%)	6 (1.3%)	12 (1.7%)
VITAMINS NOS	5 (2.1%)	7 (1.5%)	12 (1.7%)
ZOLPIDEM HEMITARTRATE	4 (1.6%)	8 (1.7%)	12 (1.7%)
AMLODIPINE	5 (2.1%)	6 (1.3%)	11 (1.5%)
ATORVASTATIN	3 (1.2%)	8 (1.7%)	11 (1.5%)
BETAMETHASONE	6 (2.5%)	5 (1.0%)	11 (1.5%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
-----	-----	-----	-----
CEFUROXIME	3 (1.2%)	8 (1.7%)	11 (1.5%)
CLOPERASTINE HYDROCHLORIDE	4 (1.6%)	7 (1.5%)	11 (1.5%)
DOXAZOSIN	6 (2.5%)	5 (1.0%)	11 (1.5%)
DOXYCYCLINE HYDROCHLORIDE	7 (2.9%)	4 (0.8%)	11 (1.5%)
GUAIFENESIN	5 (2.1%)	6 (1.3%)	11 (1.5%)
IRBESARTAN	4 (1.6%)	7 (1.5%)	11 (1.5%)
LIDOCAINE HYDROCHLORIDE	4 (1.6%)	7 (1.5%)	11 (1.5%)
LOPERAMIDE HYDROCHLORIDE	5 (2.1%)	6 (1.3%)	11 (1.5%)
METOCLOPRAMIDE	3 (1.2%)	8 (1.7%)	11 (1.5%)
ROFECOXIB	7 (2.9%)	4 (0.8%)	11 (1.5%)
SULFAMETHOXAZOLE	2 (0.8%)	9 (1.9%)	11 (1.5%)
TRIAMTERENE	6 (2.5%)	5 (1.0%)	11 (1.5%)
ACECLOFENAC	5 (2.1%)	5 (1.0%)	10 (1.4%)
ATORVASTATIN CALCIUM	8 (3.3%)	2 (0.4%)	10 (1.4%)
BROMHEXINE HYDROCHLORIDE	5 (2.1%)	5 (1.0%)	10 (1.4%)
DOMPERIDONE	2 (0.8%)	8 (1.7%)	10 (1.4%)
FAMOTIDINE	3 (1.2%)	7 (1.5%)	10 (1.4%)
GENTAMICIN SULFATE	5 (2.1%)	5 (1.0%)	10 (1.4%)
KETOPROFEN	6 (2.5%)	4 (0.8%)	10 (1.4%)
LEVOTHYROXINE SODIUM	2 (0.8%)	8 (1.7%)	10 (1.4%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040
INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
LIDOCAINE	3 (1.2%)	7 (1.5%)	10 (1.4%)
LOSARTAN POTASSIUM	2 (0.8%)	8 (1.7%)	10 (1.4%)
NIMESULIDE	3 (1.2%)	7 (1.5%)	10 (1.4%)
PERINDOPRIL	3 (1.2%)	7 (1.5%)	10 (1.4%)
PHENYLPROPANOLAMINE HYDROCHLORIDE	5 (2.1%)	5 (1.0%)	10 (1.4%)
RAMIPRIL	1 (0.4%)	9 (1.9%)	10 (1.4%)
SILDENAFIL CITRATE	1 (0.4%)	9 (1.9%)	10 (1.4%)
TETRAZEPAM	2 (0.8%)	8 (1.7%)	10 (1.4%)
VALSARTAN	3 (1.2%)	7 (1.5%)	10 (1.4%)
AMILORIDE HYDROCHLORIDE	4 (1.6%)	5 (1.0%)	9 (1.2%)
AMMONIUM CHLORIDE	3 (1.2%)	6 (1.3%)	9 (1.2%)
BUFLOMEDIL HYDROCHLORIDE	2 (0.8%)	7 (1.5%)	9 (1.2%)
CARBAMAZEPINE	2 (0.8%)	7 (1.5%)	9 (1.2%)
CEFALEXIN MONOHYDRATE	6 (2.5%)	3 (0.6%)	9 (1.2%)
CEFAZOLIN SODIUM	3 (1.2%)	6 (1.3%)	9 (1.2%)
CEFTRIAXONE	3 (1.2%)	6 (1.3%)	9 (1.2%)
CELECOXIB	1 (0.4%)	8 (1.7%)	9 (1.2%)
CETIRIZINE HYDROCHLORIDE	1 (0.4%)	8 (1.7%)	9 (1.2%)
CHLORAMPHENICOL	4 (1.6%)	5 (1.0%)	9 (1.2%)
CINEOLE	3 (1.2%)	6 (1.3%)	9 (1.2%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
DILTIAZEM	5 (2.1%)	4 (0.8%)	9 (1.2%)
DIMETICONE	2 (0.8%)	7 (1.5%)	9 (1.2%)
FELODIPINE	4 (1.6%)	5 (1.0%)	9 (1.2%)
FEXOFENADINE HYDROCHLORIDE	3 (1.2%)	6 (1.3%)	9 (1.2%)
GLIMEPIRIDE	2 (0.8%)	7 (1.5%)	9 (1.2%)
GLUCOSE	4 (1.6%)	5 (1.0%)	9 (1.2%)
MELOXICAM	5 (2.1%)	4 (0.8%)	9 (1.2%)
NAPROXEN	4 (1.6%)	5 (1.0%)	9 (1.2%)
AMITRIPTYLINE HYDROCHLORIDE	1 (0.4%)	7 (1.5%)	8 (1.1%)
BELLADONNA EXTRACT	2 (0.8%)	6 (1.3%)	8 (1.1%)
BENDROFLUMETHIAZIDE	3 (1.2%)	5 (1.0%)	8 (1.1%)
BETAMETHASONE DIPROPIONATE	4 (1.6%)	4 (0.8%)	8 (1.1%)
BISOPROLOL	1 (0.4%)	7 (1.5%)	8 (1.1%)
BROMPHENIRAMINE MALEATE	7 (2.9%)	1 (0.2%)	8 (1.1%)
CALCIUM CARBONATE	5 (2.1%)	3 (0.6%)	8 (1.1%)
CISAPRIDE	1 (0.4%)	7 (1.5%)	8 (1.1%)
CITALOPRAM	3 (1.2%)	5 (1.0%)	8 (1.1%)
CLOTTRIMAZOLE	3 (1.2%)	5 (1.0%)	8 (1.1%)
CYANOCOBALAMIN	1 (0.4%)	7 (1.5%)	8 (1.1%)
DEXTROMETHORPHAN HYDROBROMIDE	2 (0.8%)	6 (1.3%)	8 (1.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
DIHYDROCODEINE BITARTRATE	4 (1.6%)	4 (0.8%)	8 (1.1%)
ESTRADIOL	2 (0.8%)	6 (1.3%)	8 (1.1%)
EUCALYPTUS OIL	2 (0.8%)	6 (1.3%)	8 (1.1%)
FLUCONAZOLE	4 (1.6%)	4 (0.8%)	8 (1.1%)
HYDROCORTISONE	1 (0.4%)	7 (1.5%)	8 (1.1%)
MEPROBAMATE	0	8 (1.7%)	8 (1.1%)
PROPACETAMOL HYDROCHLORIDE	1 (0.4%)	7 (1.5%)	8 (1.1%)
SULPIRIDE	3 (1.2%)	5 (1.0%)	8 (1.1%)
TORASEMID	3 (1.2%)	5 (1.0%)	8 (1.1%)
TRIPROLIDINE HYDROCHLORIDE	2 (0.8%)	6 (1.3%)	8 (1.1%)
ALPRAZOLAM	4 (1.6%)	3 (0.6%)	7 (1.0%)
AMFEBUTAMONE	1 (0.4%)	6 (1.3%)	7 (1.0%)
BENZALKONIUM CHLORIDE	3 (1.2%)	4 (0.8%)	7 (1.0%)
CALCIUM PANTOTHENATE	3 (1.2%)	4 (0.8%)	7 (1.0%)
CEFOTIAM HEXETIL HYDROCHLORIDE	5 (2.1%)	2 (0.4%)	7 (1.0%)
COLCHICINE	3 (1.2%)	4 (0.8%)	7 (1.0%)
DIPOTASSIUM CLORAZEPATE	1 (0.4%)	6 (1.3%)	7 (1.0%)
EPHEDRINE HYDROCHLORIDE	4 (1.6%)	3 (0.6%)	7 (1.0%)
FLUCLOXACILLIN	1 (0.4%)	6 (1.3%)	7 (1.0%)
GLICLAZIDE	2 (0.8%)	5 (1.0%)	7 (1.0%)

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 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
HEPTAMINOL HYDROCHLORIDE	3 (1.2%)	4 (0.8%)	7 (1.0%)
HYOSCINE BUTYLBROMIDE	4 (1.6%)	3 (0.6%)	7 (1.0%)
INDAPAMIDE	1 (0.4%)	6 (1.3%)	7 (1.0%)
INDOMETACIN	3 (1.2%)	4 (0.8%)	7 (1.0%)
METFORMIN	0 .	7 (1.5%)	7 (1.0%)
METOPROLOL SUCCINATE	0 .	7 (1.5%)	7 (1.0%)
MOMETASONE FUROATE	4 (1.6%)	3 (0.6%)	7 (1.0%)
NAPHAZOLINE NITRATE	3 (1.2%)	4 (0.8%)	7 (1.0%)
OXITROPIUM BROMIDE	4 (1.6%)	3 (0.6%)	7 (1.0%)
PAROXETINE	4 (1.6%)	3 (0.6%)	7 (1.0%)
PENTOXIFYLLINE	2 (0.8%)	5 (1.0%)	7 (1.0%)
RIBOFLAVIN	4 (1.6%)	3 (0.6%)	7 (1.0%)
SALICYLIC ACID	3 (1.2%)	4 (0.8%)	7 (1.0%)
SERENOA REPENS	4 (1.6%)	3 (0.6%)	7 (1.0%)
TIAPROFENIC ACID	3 (1.2%)	4 (0.8%)	7 (1.0%)
TOBRAMYCIN	4 (1.6%)	3 (0.6%)	7 (1.0%)
TRIFLUSAL	3 (1.2%)	4 (0.8%)	7 (1.0%)
TROXERUTIN	3 (1.2%)	4 (0.8%)	7 (1.0%)
ACENOCOUMAROL	0 .	6 (1.3%)	6 (0.8%)
ATENOLOL	3 (1.2%)	3 (0.6%)	6 (0.8%)

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SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
ATROPINE SULFATE	3 (1.2%)	3 (0.6%)	6 (0.8%)
ATTAPULGITE	2 (0.8%)	4 (0.8%)	6 (0.8%)
BENZOIC ACID	3 (1.2%)	3 (0.6%)	6 (0.8%)
BUMETANIDE	1 (0.4%)	5 (1.0%)	6 (0.8%)
CETRIMONIUM BROMIDE	3 (1.2%)	3 (0.6%)	6 (0.8%)
DIPHENOXYLATE HYDROCHLORIDE	3 (1.2%)	3 (0.6%)	6 (0.8%)
FENSPIRIDE HYDROCHLORIDE	2 (0.8%)	4 (0.8%)	6 (0.8%)
FOLIC ACID	1 (0.4%)	5 (1.0%)	6 (0.8%)
GUAIACOL	2 (0.8%)	4 (0.8%)	6 (0.8%)
KETOROLAC TROMETHAMINE	4 (1.6%)	2 (0.4%)	6 (0.8%)
LORMETAZEPAM	2 (0.8%)	4 (0.8%)	6 (0.8%)
MAGNESIUM HYDROXIDE	2 (0.8%)	4 (0.8%)	6 (0.8%)
MAGNESIUM OXIDE	2 (0.8%)	4 (0.8%)	6 (0.8%)
MICONAZOLE NITRATE	3 (1.2%)	3 (0.6%)	6 (0.8%)
MINERALS NOS	2 (0.8%)	4 (0.8%)	6 (0.8%)
NAPROXEN SODIUM	3 (1.2%)	3 (0.6%)	6 (0.8%)
NICOTINAMIDE	4 (1.6%)	2 (0.4%)	6 (0.8%)
NITRENDIPINE	2 (0.8%)	4 (0.8%)	6 (0.8%)
NORFLOXACIN	0 .	6 (1.3%)	6 (0.8%)
PHENOXYMETHYLPENICILLIN POTASSIUM	3 (1.2%)	3 (0.6%)	6 (0.8%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
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GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
PIROXICAM BETA CYCLODEXTRIN	3 (1.2%)	3 (0.6%)	6 (0.8%)
POLYMYXIN B SULFATE	3 (1.2%)	3 (0.6%)	6 (0.8%)
PRAVASTATIN	2 (0.8%)	4 (0.8%)	6 (0.8%)
SODIUM CAMSYLATE	2 (0.8%)	4 (0.8%)	6 (0.8%)
TERAZOSIN HYDROCHLORIDE	1 (0.4%)	5 (1.0%)	6 (0.8%)
TRIAMCINOLONE	0 .	6 (1.3%)	6 (0.8%)
VERAPAMIL	2 (0.8%)	4 (0.8%)	6 (0.8%)
ACICLOVIR	0 .	5 (1.0%)	5 (0.7%)
ALENDRONATE	1 (0.4%)	4 (0.8%)	5 (0.7%)
ALFUZOSIN HYDROCHLORIDE	1 (0.4%)	4 (0.8%)	5 (0.7%)
AZELASTINE	2 (0.8%)	3 (0.6%)	5 (0.7%)
BACITRACIN	1 (0.4%)	4 (0.8%)	5 (0.7%)
BECLOMETASONE	2 (0.8%)	3 (0.6%)	5 (0.7%)
BISACODYL	3 (1.2%)	2 (0.4%)	5 (0.7%)
CAFFEINE CITRATE	2 (0.8%)	3 (0.6%)	5 (0.7%)
CAMPHOR	1 (0.4%)	4 (0.8%)	5 (0.7%)
CANDESARTAN CILEXETIL	1 (0.4%)	4 (0.8%)	5 (0.7%)
CARQUEJA	2 (0.8%)	3 (0.6%)	5 (0.7%)
CEFALEXIN	1 (0.4%)	4 (0.8%)	5 (0.7%)
CEFUROXIME SODIUM	3 (1.2%)	2 (0.4%)	5 (0.7%)

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SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
COLECALCIFEROL	2 (0.8%)	3 (0.6%)	5 (0.7%)
DIPHENHYDRAMINE HYDROCHLORIDE	2 (0.8%)	3 (0.6%)	5 (0.7%)
DIPHENYLPYRALINE HYDROCHLORIDE	2 (0.8%)	3 (0.6%)	5 (0.7%)
ERDOSTEINE	3 (1.2%)	2 (0.4%)	5 (0.7%)
FENOXAZOLINE HYDROCHLORIDE	2 (0.8%)	3 (0.6%)	5 (0.7%)
FERROUS SULFATE	1 (0.4%)	4 (0.8%)	5 (0.7%)
FRAMYCETIN SULFATE	0 .	5 (1.0%)	5 (0.7%)
GINKGO TREE LEAVES EXTRACT	1 (0.4%)	4 (0.8%)	5 (0.7%)
HEPARIN-FRACTION, SODIUM SALT	1 (0.4%)	4 (0.8%)	5 (0.7%)
INSULIN HUMAN	0 .	5 (1.0%)	5 (0.7%)
IPECACUANHA	2 (0.8%)	3 (0.6%)	5 (0.7%)
LYSOZYME	1 (0.4%)	4 (0.8%)	5 (0.7%)
METOCLOPRAMIDE HYDROCHLORIDE	2 (0.8%)	3 (0.6%)	5 (0.7%)
MIKANIA GLOMERATA	2 (0.8%)	3 (0.6%)	5 (0.7%)
NAFTIDROFURYL OXALATE	0 .	5 (1.0%)	5 (0.7%)
NEBIVOLOL HYDROCHLORIDE	2 (0.8%)	3 (0.6%)	5 (0.7%)
NORETHISTERONE ACETATE	1 (0.4%)	4 (0.8%)	5 (0.7%)
PANTOPRAZOL	2 (0.8%)	3 (0.6%)	5 (0.7%)
PAPAIN	1 (0.4%)	4 (0.8%)	5 (0.7%)
PARAFFIN, SOFT	1 (0.4%)	4 (0.8%)	5 (0.7%)

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GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
PHENOBARBITAL	2 (0.8%)	3 (0.6%)	5 (0.7%)
PHENYLEPHRINE	3 (1.2%)	2 (0.4%)	5 (0.7%)
PROPYPHENAZONE	1 (0.4%)	4 (0.8%)	5 (0.7%)
PYGEUM AFRICANUM	2 (0.8%)	3 (0.6%)	5 (0.7%)
REPROTEROL HYDROCHLORIDE	1 (0.4%)	4 (0.8%)	5 (0.7%)
RETINOL	3 (1.2%)	2 (0.4%)	5 (0.7%)
SACCHARIN SODIUM	1 (0.4%)	4 (0.8%)	5 (0.7%)
SUCRALFATE	2 (0.8%)	3 (0.6%)	5 (0.7%)
TEMAZEPAM	1 (0.4%)	4 (0.8%)	5 (0.7%)
TIXOCORTOL PIVALATE	2 (0.8%)	3 (0.6%)	5 (0.7%)
TOLTERODINE	3 (1.2%)	2 (0.4%)	5 (0.7%)
TRANDOLAPRILAT	3 (1.2%)	2 (0.4%)	5 (0.7%)
TUAMINOHEPTANE SULFATE	2 (0.8%)	3 (0.6%)	5 (0.7%)
WARFARIN SODIUM	3 (1.2%)	2 (0.4%)	5 (0.7%)
ACARBOSE	2 (0.8%)	2 (0.4%)	4 (0.6%)
ACETAZOLAMIDE	2 (0.8%)	2 (0.4%)	4 (0.6%)
ACETYLDIGOXIN	3 (1.2%)	1 (0.2%)	4 (0.6%)
ALUMINIUM HYDROXIDE-MAGNESIUM CARBONATE	1 (0.4%)	3 (0.6%)	4 (0.6%)
AMINOACETIC ACID	2 (0.8%)	2 (0.4%)	4 (0.6%)
ATROPINE BORATE	2 (0.8%)	2 (0.4%)	4 (0.6%)

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GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
BENZOCAINE	2 (0.8%)	2 (0.4%)	4 (0.6%)
BEZAFIBRATE	2 (0.8%)	2 (0.4%)	4 (0.6%)
BISOPROLOL FUMARATE	1 (0.4%)	3 (0.6%)	4 (0.6%)
BRIMONIDINE TARTRATE	0 .	4 (0.8%)	4 (0.6%)
CALCIUM	0 .	4 (0.8%)	4 (0.6%)
CARVEDILOL	1 (0.4%)	3 (0.6%)	4 (0.6%)
CEFETAMET	1 (0.4%)	3 (0.6%)	4 (0.6%)
CEFIXIME TRIHYDRATE	1 (0.4%)	3 (0.6%)	4 (0.6%)
CERIVASTATIN	2 (0.8%)	2 (0.4%)	4 (0.6%)
CHLORHEXIDINE GLUCONATE	2 (0.8%)	2 (0.4%)	4 (0.6%)
CHLOROBUTANOL	3 (1.2%)	1 (0.2%)	4 (0.6%)
CIMETIDINE	1 (0.4%)	3 (0.6%)	4 (0.6%)
CLOBETASONE BUTYRATE	0 .	4 (0.8%)	4 (0.6%)
COCARBOXYLASE	1 (0.4%)	3 (0.6%)	4 (0.6%)
CROMOGLICATE SODIUM	1 (0.4%)	3 (0.6%)	4 (0.6%)
DEANOL PIDOLATE	3 (1.2%)	1 (0.2%)	4 (0.6%)
DEXCHLORPHENIRAMINE MALEATE	0 .	4 (0.8%)	4 (0.6%)
DICLOFENAC DIETHYLAMINE	1 (0.4%)	3 (0.6%)	4 (0.6%)
DIETHYLAMINE SALICYLATE	2 (0.8%)	2 (0.4%)	4 (0.6%)
DIMETICONE, ACTIVATED	2 (0.8%)	2 (0.4%)	4 (0.6%)

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GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
DIMETOTIAZINE	2 (0.8%)	2 (0.4%)	4 (0.6%)
DOCUSATE SODIUM	1 (0.4%)	3 (0.6%)	4 (0.6%)
DOXYCYCLINE HYCLATE	2 (0.8%)	2 (0.4%)	4 (0.6%)
EBASTINE	1 (0.4%)	3 (0.6%)	4 (0.6%)
ESTROGENS CONJUGATED	1 (0.4%)	3 (0.6%)	4 (0.6%)
FLUINDIONE	1 (0.4%)	3 (0.6%)	4 (0.6%)
FLUOCINOLONE ACETONIDE	0 .	4 (0.8%)	4 (0.6%)
FUROSEMIDE XANTINOL	3 (1.2%)	1 (0.2%)	4 (0.6%)
FUSAFUNGINE	1 (0.4%)	3 (0.6%)	4 (0.6%)
FUSIDATE SODIUM	2 (0.8%)	2 (0.4%)	4 (0.6%)
FUSIDIC ACID	2 (0.8%)	2 (0.4%)	4 (0.6%)
GEMFIBROZIL	0 .	4 (0.8%)	4 (0.6%)
GENTAMICIN	1 (0.4%)	3 (0.6%)	4 (0.6%)
GRAMICIDIN	1 (0.4%)	3 (0.6%)	4 (0.6%)
HEPARIN	0 .	4 (0.8%)	4 (0.6%)
HESPERIDIN METHYL CHALCONE	2 (0.8%)	2 (0.4%)	4 (0.6%)
HEXETIDINE	2 (0.8%)	2 (0.4%)	4 (0.6%)
HYDROCORTISONE BUTYRATE	3 (1.2%)	1 (0.2%)	4 (0.6%)
INSULIN INJECTION, ISOPHANE	0 .	4 (0.8%)	4 (0.6%)
LIQUORICE LIQUID EXTRACT	1 (0.4%)	3 (0.6%)	4 (0.6%)

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GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
LOPERAMIDE	0 .	4 (0.8%)	4 (0.6%)
MAGNESIUM NOS	1 (0.4%)	3 (0.6%)	4 (0.6%)
MEPYRAMINE THEOPHYLLINE ACETATE	0 .	4 (0.8%)	4 (0.6%)
METOPROLOL	1 (0.4%)	3 (0.6%)	4 (0.6%)
MONTMORILLONITE BEIDELLITIQUE	3 (1.2%)	1 (0.2%)	4 (0.6%)
MORPHINE	0 .	4 (0.8%)	4 (0.6%)
NIAOULI OIL	2 (0.8%)	2 (0.4%)	4 (0.6%)
NIFLUMIC ACID	2 (0.8%)	2 (0.4%)	4 (0.6%)
NIMODIPINE	1 (0.4%)	3 (0.6%)	4 (0.6%)
PARAFFIN, LIQUID	1 (0.4%)	3 (0.6%)	4 (0.6%)
PENTOSAN POLYSULFATE	2 (0.8%)	2 (0.4%)	4 (0.6%)
PHLOROGLUCINOL	1 (0.4%)	3 (0.6%)	4 (0.6%)
POLYVIDONE	1 (0.4%)	3 (0.6%)	4 (0.6%)
PROPOFOL	1 (0.4%)	3 (0.6%)	4 (0.6%)
PYRIDOXINE	1 (0.4%)	3 (0.6%)	4 (0.6%)
RAUBASINE	1 (0.4%)	3 (0.6%)	4 (0.6%)
RILMENIDINE PHOSPHATE	2 (0.8%)	2 (0.4%)	4 (0.6%)
SACCHAROMYCES BOULARDII	0 .	4 (0.8%)	4 (0.6%)
SERTRALINE	0 .	4 (0.8%)	4 (0.6%)
SMECTITE	1 (0.4%)	3 (0.6%)	4 (0.6%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
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3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
SOTALOL HYDROCHLORIDE	1 (0.4%)	3 (0.6%)	4 (0.6%)
TETANUS TOXOID	0 .	4 (0.8%)	4 (0.6%)
THIOLCHICOSIDE	1 (0.4%)	3 (0.6%)	4 (0.6%)
TIANEPTINE	2 (0.8%)	2 (0.4%)	4 (0.6%)
TRAMADOL	2 (0.8%)	2 (0.4%)	4 (0.6%)
TRIMETAZIDINE DIHYDROCHLORIDE	1 (0.4%)	3 (0.6%)	4 (0.6%)
TRIMETHYLPHLOROGLUCINOL	1 (0.4%)	3 (0.6%)	4 (0.6%)
VANILLINE	1 (0.4%)	3 (0.6%)	4 (0.6%)
VENLAFAXINE	2 (0.8%)	2 (0.4%)	4 (0.6%)
WARFARIN	3 (1.2%)	1 (0.2%)	4 (0.6%)
ACEXAMATE ZINC	1 (0.4%)	2 (0.4%)	3 (0.4%)
ADRENAL CORTICAL EXTRACT	1 (0.4%)	2 (0.4%)	3 (0.4%)
ALFUZOSIN	1 (0.4%)	2 (0.4%)	3 (0.4%)
ALMITRINE DIMESILATE	1 (0.4%)	2 (0.4%)	3 (0.4%)
ALTIZIDE	0 .	3 (0.6%)	3 (0.4%)
AMANTADINE HYDROCHLORIDE	2 (0.8%)	1 (0.2%)	3 (0.4%)
AMINOPHYLLINE	1 (0.4%)	2 (0.4%)	3 (0.4%)
AMIODARONE	0 .	3 (0.6%)	3 (0.4%)
AMITRIPTYLINE	1 (0.4%)	2 (0.4%)	3 (0.4%)
AMOBARBITAL	0 .	3 (0.6%)	3 (0.4%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

SB 207499

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
AMPHOTERICIN B	2 (0.8%)	1 (0.2%)	3 (0.4%)
ANTIBIOTIC NOS	1 (0.4%)	2 (0.4%)	3 (0.4%)
BACAMPICILLIN HYDROCHLORIDE	0 .	3 (0.6%)	3 (0.4%)
BETAHISTINE HYDROCHLORIDE	2 (0.8%)	1 (0.2%)	3 (0.4%)
CARBASALATE CALCIUM	1 (0.4%)	2 (0.4%)	3 (0.4%)
CARBIMAZOLE	0 .	3 (0.6%)	3 (0.4%)
CARBOMER	2 (0.8%)	1 (0.2%)	3 (0.4%)
CEFONICIDE SODIUM	1 (0.4%)	2 (0.4%)	3 (0.4%)
CEFTIBUTEN	0 .	3 (0.6%)	3 (0.4%)
CELIPROLOL HYDROCHLORIDE	0 .	3 (0.6%)	3 (0.4%)
CHLORTALIDONE	1 (0.4%)	2 (0.4%)	3 (0.4%)
CITRIC ACID	0 .	3 (0.6%)	3 (0.4%)
CLEBOPRIDE	2 (0.8%)	1 (0.2%)	3 (0.4%)
CLEMASTINE FUMARATE	2 (0.8%)	1 (0.2%)	3 (0.4%)
CLINDAMYCIN HYDROCHLORIDE	1 (0.4%)	2 (0.4%)	3 (0.4%)
CLONIXIN LYSINATE	2 (0.8%)	1 (0.2%)	3 (0.4%)
CLOXACILLIN SODIUM	1 (0.4%)	2 (0.4%)	3 (0.4%)
CODEINE HYDROCHLORIDE	2 (0.8%)	1 (0.2%)	3 (0.4%)
CYCLOPENTOLATE HYDROCHLORIDE	1 (0.4%)	2 (0.4%)	3 (0.4%)
DALTEPARINE	1 (0.4%)	2 (0.4%)	3 (0.4%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
DESIPRAMINE HYDROCHLORIDE	1 (0.4%)	2 (0.4%)	3 (0.4%)
DEXAMETHASONE SODIUM PHOSPHATE	2 (0.8%)	1 (0.2%)	3 (0.4%)
DIOSMIN	1 (0.4%)	2 (0.4%)	3 (0.4%)
DIPROPHYLLINE	0 .	3 (0.6%)	3 (0.4%)
DORZOLAMIDE HYDROCHLORIDE	0 .	3 (0.6%)	3 (0.4%)
DOSULEPIN	1 (0.4%)	2 (0.4%)	3 (0.4%)
DOXAZOSIN MESYLATE	1 (0.4%)	2 (0.4%)	3 (0.4%)
EMULSIFYING WAX	1 (0.4%)	2 (0.4%)	3 (0.4%)
ERYTHROMYCIN STEARATE	0 .	3 (0.6%)	3 (0.4%)
ESTRADIOL VALERATE	1 (0.4%)	2 (0.4%)	3 (0.4%)
ETHYLMORPHINE HYDROCHLORIDE	2 (0.8%)	1 (0.2%)	3 (0.4%)
FENTANYL	0 .	3 (0.6%)	3 (0.4%)
FLUDROCORTISONE ACETATE	2 (0.8%)	1 (0.2%)	3 (0.4%)
FLUNISOLIDE	0 .	3 (0.6%)	3 (0.4%)
FLUNITRAZEPAM	1 (0.4%)	2 (0.4%)	3 (0.4%)
FLUVASTATIN SODIUM	1 (0.4%)	2 (0.4%)	3 (0.4%)
FOSINOPRIL	3 (1.2%)	0 .	3 (0.4%)
GENTIAN	0 .	3 (0.6%)	3 (0.4%)
GLUCOSAMINE	0 .	3 (0.6%)	3 (0.4%)
GLUTAMIC ACID	1 (0.4%)	2 (0.4%)	3 (0.4%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
HALAZEPAM	0 .	3 (0.6%)	3 (0.4%)
HELICIDINE	1 (0.4%)	2 (0.4%)	3 (0.4%)
HEXOPRENALINE SULFATE	2 (0.8%)	1 (0.2%)	3 (0.4%)
HYDROXOCOBALAMIN	2 (0.8%)	1 (0.2%)	3 (0.4%)
HYOSCYAMINE SULFATE	0 .	3 (0.6%)	3 (0.4%)
HYPERICUM EXTRACT	0 .	3 (0.6%)	3 (0.4%)
HYPROMELLOSE	2 (0.8%)	1 (0.2%)	3 (0.4%)
INOSINE	0 .	3 (0.6%)	3 (0.4%)
INSULIN	1 (0.4%)	2 (0.4%)	3 (0.4%)
ISPAGHULA	1 (0.4%)	2 (0.4%)	3 (0.4%)
KETOCONAZOLE	2 (0.8%)	1 (0.2%)	3 (0.4%)
LACTITOL MONOHYDRATE	2 (0.8%)	1 (0.2%)	3 (0.4%)
LATANOPROST	0 .	3 (0.6%)	3 (0.4%)
LERCANIDIPINE	2 (0.8%)	1 (0.2%)	3 (0.4%)
LEVONORGESTREL	0 .	3 (0.6%)	3 (0.4%)
LYMECYCLINE	1 (0.4%)	2 (0.4%)	3 (0.4%)
MACROGOL	2 (0.8%)	1 (0.2%)	3 (0.4%)
MAGNESIUM CARBONATE	0 .	3 (0.6%)	3 (0.4%)
MAGNESIUM GLUTAMATE	3 (1.2%)	0 .	3 (0.4%)
MEBEVERINE	1 (0.4%)	2 (0.4%)	3 (0.4%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
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4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
MESNA	3 (1.2%)	0 .	3 (0.4%)
METHYLPREDNISOLONE ACEPONATE	0 .	3 (0.6%)	3 (0.4%)
METHYLPREDNISOLONE ACETATE	3 (1.2%)	0 .	3 (0.4%)
MIDAZOLAM MALEATE	3 (1.2%)	0 .	3 (0.4%)
MIZOLASTINE	2 (0.8%)	1 (0.2%)	3 (0.4%)
MONTELUKAST SODIUM	1 (0.4%)	2 (0.4%)	3 (0.4%)
MORPHINE SULFATE	1 (0.4%)	2 (0.4%)	3 (0.4%)
NICOTINE	2 (0.8%)	1 (0.2%)	3 (0.4%)
NIFUROXAZIDE	2 (0.8%)	1 (0.2%)	3 (0.4%)
NITRAZEPAM	1 (0.4%)	2 (0.4%)	3 (0.4%)
OXAZEPAM	0 .	3 (0.6%)	3 (0.4%)
OXETACAINE	0 .	3 (0.6%)	3 (0.4%)
OXYMETAZOLINE HYDROCHLORIDE	0 .	3 (0.6%)	3 (0.4%)
OXYTETRACYCLINE	2 (0.8%)	1 (0.2%)	3 (0.4%)
OXYTETRACYCLINE CALCIUM	0 .	3 (0.6%)	3 (0.4%)
PANCREATIN	2 (0.8%)	1 (0.2%)	3 (0.4%)
PENTOSAN POLYSULFATE SODIUM	0 .	3 (0.6%)	3 (0.4%)
PENTOXYVERINE CITRATE	0 .	3 (0.6%)	3 (0.4%)
PHENPROCUMON	1 (0.4%)	2 (0.4%)	3 (0.4%)
PINE OIL	1 (0.4%)	2 (0.4%)	3 (0.4%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
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TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
PIRETANIDE	1 (0.4%)	2 (0.4%)	3 (0.4%)
POTASSIUM ASCORBATE	1 (0.4%)	2 (0.4%)	3 (0.4%)
PRAVASTATIN SODIUM	2 (0.8%)	1 (0.2%)	3 (0.4%)
PRazosin	1 (0.4%)	2 (0.4%)	3 (0.4%)
PREDNISOLONE ACETATE	1 (0.4%)	2 (0.4%)	3 (0.4%)
PRIMULA FLOWERS	0 .	3 (0.6%)	3 (0.4%)
PROPRANOLOL	1 (0.4%)	2 (0.4%)	3 (0.4%)
PSEUDOEPHEDRINE	2 (0.8%)	1 (0.2%)	3 (0.4%)
QUININE	1 (0.4%)	2 (0.4%)	3 (0.4%)
QUININE BENZOATE	2 (0.8%)	1 (0.2%)	3 (0.4%)
RUSCUS ACULEATUS	1 (0.4%)	2 (0.4%)	3 (0.4%)
SENNOSIDE A+B	0 .	3 (0.6%)	3 (0.4%)
SODIUM BENZOATE	0 .	3 (0.6%)	3 (0.4%)
SODIUM LACTATE COMPOUND INJECTION	1 (0.4%)	2 (0.4%)	3 (0.4%)
SODIUM PHOSPHATE DIBASIC	2 (0.8%)	1 (0.2%)	3 (0.4%)
STERCULIA	0 .	3 (0.6%)	3 (0.4%)
SULFADIAZINE	1 (0.4%)	2 (0.4%)	3 (0.4%)
TELITHROMYCIN	0 .	3 (0.6%)	3 (0.4%)
TERBINAFINE	1 (0.4%)	2 (0.4%)	3 (0.4%)
TERBUTALINE	0 .	3 (0.6%)	3 (0.4%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
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TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
TERPIN HYDRATE	1 (0.4%)	2 (0.4%)	3 (0.4%)
THIAMPHENICOL	3 (1.2%)	0 .	3 (0.4%)
TIEMONIUM METHYLSULFATE	0 .	3 (0.6%)	3 (0.4%)
TOCOPHEROL	2 (0.8%)	1 (0.2%)	3 (0.4%)
TURPENTINE OIL	1 (0.4%)	2 (0.4%)	3 (0.4%)
VALERIAN ROOT	1 (0.4%)	2 (0.4%)	3 (0.4%)
VENLAFAXINE HYDROCHLORIDE	2 (0.8%)	1 (0.2%)	3 (0.4%)
VERBENA HERB	0 .	3 (0.6%)	3 (0.4%)
ZINC OXIDE	0 .	3 (0.6%)	3 (0.4%)
ACEGLUTAMIDE	0 .	2 (0.4%)	2 (0.3%)
ACETYL ASPARTIC ACID	0 .	2 (0.4%)	2 (0.3%)
ACRIVASTINE	2 (0.8%)	0 .	2 (0.3%)
ALANINE	1 (0.4%)	1 (0.2%)	2 (0.3%)
ALLANTOIN	0 .	2 (0.4%)	2 (0.3%)
ALMASILATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
ALUMINIUM	0 .	2 (0.4%)	2 (0.3%)
ALUMINIUM GLYCINATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
ALVERINE CITRATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
AMPICILLIN SODIUM	0 .	2 (0.4%)	2 (0.3%)
ASPARTATE MAGNESIUM	0 .	2 (0.4%)	2 (0.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
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TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
BETAXOLOL	0 .	2 (0.4%)	2 (0.3%)
BETAXOLOL HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)
BEVONIUM METILSULFATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
BISMUTH	0 .	2 (0.4%)	2 (0.3%)
BROMELAINS	0 .	2 (0.4%)	2 (0.3%)
BUPIVACAINE	0 .	2 (0.4%)	2 (0.3%)
BUTALBITAL	0 .	2 (0.4%)	2 (0.3%)
BUZEPIDE METHYLHYDROXIDE	0 .	2 (0.4%)	2 (0.3%)
CALCIFEDIOL	2 (0.8%)	0 .	2 (0.3%)
CARBOHYDRATE	0 .	2 (0.4%)	2 (0.3%)
CARRAGHENATE	0 .	2 (0.4%)	2 (0.3%)
CEFADROXIL	1 (0.4%)	1 (0.2%)	2 (0.3%)
CEFADROXIL MONOHYDRATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
CEFATRIZINE	1 (0.4%)	1 (0.2%)	2 (0.3%)
CEFAZOLIN	0 .	2 (0.4%)	2 (0.3%)
CETIRIZINE	0 .	2 (0.4%)	2 (0.3%)
CHLORCYCLIZINE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)
CHLORDIAZEPOXIDE	2 (0.8%)	0 .	2 (0.3%)
CHLORDIAZEPOXIDE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)
CHLORPROMAZINE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
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TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
CIBENZOLINE SUCCINATE	0 .	2 (0.4%)	2 (0.3%)
CINCHOCAINE HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
CINITAPRIDE	0 .	2 (0.4%)	2 (0.3%)
CITRULLINE	0 .	2 (0.4%)	2 (0.3%)
CLOBAZAM	0 .	2 (0.4%)	2 (0.3%)
CLOBETASOL PROPIONATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
CLOMIPRAMINE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)
CLONAZEPAM	0 .	2 (0.4%)	2 (0.3%)
CLONIDINE HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
COCILLANA LIQUID EXTRACT	2 (0.8%)	0 .	2 (0.3%)
CRATAEGUS	0 .	2 (0.4%)	2 (0.3%)
CYSTINE	0 .	2 (0.4%)	2 (0.3%)
DANTRON	1 (0.4%)	1 (0.2%)	2 (0.3%)
DEXTROMETHORPHAN	1 (0.4%)	1 (0.2%)	2 (0.3%)
DIACEREIN	1 (0.4%)	1 (0.2%)	2 (0.3%)
DICLOFENAC POTASSIUM	0 .	2 (0.4%)	2 (0.3%)
DIFLUCORTOLONE VALERATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
DIHYDROERGOCRISTINE MESILATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
DIHYDROERGOTAMINE MESILATE	0 .	2 (0.4%)	2 (0.3%)
DIPYRIDAMOLE	0 .	2 (0.4%)	2 (0.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
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TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
DOXEPIN	1 (0.4%)	1 (0.2%)	2 (0.3%)
DOXEPIN HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
ECONAZOLE NITRATE	0 .	2 (0.4%)	2 (0.3%)
EMSER SALT	0 .	2 (0.4%)	2 (0.3%)
EPINEPHRINE	0 .	2 (0.4%)	2 (0.3%)
ERYTHROMYCIN ETHYLSUCCINATE	0 .	2 (0.4%)	2 (0.3%)
ESCULIN	1 (0.4%)	1 (0.2%)	2 (0.3%)
ESTRIOL	0 .	2 (0.4%)	2 (0.3%)
ETHINYLESTRADIOL	0 .	2 (0.4%)	2 (0.3%)
ETHYLENEDIAMINE	1 (0.4%)	1 (0.2%)	2 (0.3%)
ETILEFRINE HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
FAT	0 .	2 (0.4%)	2 (0.3%)
FLECAINIDE ACETATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
FLUNARIZINE DIHYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)
FLUPENTIXOL	1 (0.4%)	1 (0.2%)	2 (0.3%)
FLURAZEPAM HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
GINSENG	0 .	2 (0.4%)	2 (0.3%)
GLIPIZIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
GLYCEROL	0 .	2 (0.4%)	2 (0.3%)
GOSERELIN	0 .	2 (0.4%)	2 (0.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
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TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
HALOPERIDOL	0 .	2 (0.4%)	2 (0.3%)
HERBAL EXTRACTS NOS	0 .	2 (0.4%)	2 (0.3%)
HEXAMIDINE ISETHIONATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
HYDROCODONE BITARTRATE	0 .	2 (0.4%)	2 (0.3%)
HYDROCORTISONE ACETATE	0 .	2 (0.4%)	2 (0.3%)
HYDROCORTISONE SODIUM PHOSPHATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
HYDROXYETHYLCELLULOSE	2 (0.8%)	0 .	2 (0.3%)
IMMUNOGLOBULIN HUMAN NORMAL	2 (0.8%)	0 .	2 (0.3%)
INSULIN HUMAN INJECTION, ISOPHANE	0 .	2 (0.4%)	2 (0.3%)
KETAZOLAM	1 (0.4%)	1 (0.2%)	2 (0.3%)
LACIDIPINE	0 .	2 (0.4%)	2 (0.3%)
LACTITOL	0 .	2 (0.4%)	2 (0.3%)
LEVOCABASTINE HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
LOCAL ANESTHESIA	1 (0.4%)	1 (0.2%)	2 (0.3%)
LOPRAZOLAM MESILATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
MAGNESIUM LACTATE	0 .	2 (0.4%)	2 (0.3%)
MAGNESIUM SULFATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
MEBEVERINE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)
MEDAZEPAM	0 .	2 (0.4%)	2 (0.3%)
MELITRACEN	1 (0.4%)	1 (0.2%)	2 (0.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
MEPYRAMINE MALEATE	0 .	2 (0.4%)	2 (0.3%)
METFORMIN EMBONATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
METHENAMINE HIPPURATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
METHOTREXATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
METOPROLOL TARTRATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
METRONIDAZOLE	1 (0.4%)	1 (0.2%)	2 (0.3%)
MIANSERIN HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
MICONAZOLE	1 (0.4%)	1 (0.2%)	2 (0.3%)
MIGLITOL	0 .	2 (0.4%)	2 (0.3%)
MOROXYDINE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)
MORPHINE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)
MUCOPOLYSACCHARIDE POLYSULFURIC ACID ESTER	1 (0.4%)	1 (0.2%)	2 (0.3%)
MULTIVITAMINS, NOS	1 (0.4%)	1 (0.2%)	2 (0.3%)
MUPIROCIN	2 (0.8%)	0 .	2 (0.3%)
MYRTILLUS	1 (0.4%)	1 (0.2%)	2 (0.3%)
NABUMETONE	0 .	2 (0.4%)	2 (0.3%)
NICARDIPINE HYDROCHLORIDE	2 (0.8%)	0 .	2 (0.3%)
NICORANDIL	1 (0.4%)	1 (0.2%)	2 (0.3%)
NICOTINE RESIN	1 (0.4%)	1 (0.2%)	2 (0.3%)
NIZATIDINE	1 (0.4%)	1 (0.2%)	2 (0.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040
INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

SB 207499

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
NORAMIDOPYRINE METHANESULFONATE MAGNESIUM	1 (0.4%)	1 (0.2%)	2 (0.3%)
NOSCAPINE	1 (0.4%)	1 (0.2%)	2 (0.3%)
NUTRITIONAL SUPPLEMENT NOS	1 (0.4%)	1 (0.2%)	2 (0.3%)
OINTMENT	2 (0.8%)	0 .	2 (0.3%)
OMEPRAZOLE SODIUM	0 .	2 (0.4%)	2 (0.3%)
OPIUM	0 .	2 (0.4%)	2 (0.3%)
OXYBUTYNIN	1 (0.4%)	1 (0.2%)	2 (0.3%)
OXYTETRACYCLINE HYDROCHLORIDE	2 (0.8%)	0 .	2 (0.3%)
PANTOPRAZOLE SODIUM	0 .	2 (0.4%)	2 (0.3%)
PAPAVERINE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)
PECTIN	2 (0.8%)	0 .	2 (0.3%)
PENICILLIN NOS	1 (0.4%)	1 (0.2%)	2 (0.3%)
PHENAZONE	0 .	2 (0.4%)	2 (0.3%)
PHENOXYMETHYLPENICILLIN	0 .	2 (0.4%)	2 (0.3%)
PIAS	0 .	2 (0.4%)	2 (0.3%)
PIPEMIDIC ACID	2 (0.8%)	0 .	2 (0.3%)
POLYVINYL ALCOHOL	2 (0.8%)	0 .	2 (0.3%)
POTASSIUM MAGNESIUM ASPARTATE	0 .	2 (0.4%)	2 (0.3%)
POVIDONE-IODINE	0 .	2 (0.4%)	2 (0.3%)
PRAZOSIN HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040
INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
PROPAFENONE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)
PROTEIN	0 .	2 (0.4%)	2 (0.3%)
PRUNUS AFRICANA	1 (0.4%)	1 (0.2%)	2 (0.3%)
PSEUDOEPHEDRINE SULFATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
PYRIDOXAL PHOSPHATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
QUINAPRIL	2 (0.8%)	0 .	2 (0.3%)
QUINAPRIL HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
QUININE HYDROCHLORIDE	2 (0.8%)	0 .	2 (0.3%)
REBOXETINE	0 .	2 (0.4%)	2 (0.3%)
RUMICIS ASETOSA	0 .	2 (0.4%)	2 (0.3%)
RUTOSIDE	0 .	2 (0.4%)	2 (0.3%)
SABAL EXTRACT	0 .	2 (0.4%)	2 (0.3%)
SACCHAROSE	0 .	2 (0.4%)	2 (0.3%)
SAMBUCUS FLOWERS	0 .	2 (0.4%)	2 (0.3%)
SENNA	1 (0.4%)	1 (0.2%)	2 (0.3%)
SERINE PHOSPHATE	0 .	2 (0.4%)	2 (0.3%)
SILVER NITRATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
SODIUM PHOSPHATE MONOBASIC	2 (0.8%)	0 .	2 (0.3%)
SULFOGAIACOL	0 .	2 (0.4%)	2 (0.3%)
SUPROFEN	1 (0.4%)	1 (0.2%)	2 (0.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
-----	-----	-----	-----
TELMISARTAN	1 (0.4%)	1 (0.2%)	2 (0.3%)
TENOXICAM	1 (0.4%)	1 (0.2%)	2 (0.3%)
TETRYZOLINE HYDROCHLORIDE	2 (0.8%)	0 .	2 (0.3%)
THIAMAZOLE	1 (0.4%)	1 (0.2%)	2 (0.3%)
THIAMINE	1 (0.4%)	1 (0.2%)	2 (0.3%)
THIAMINE MONONITRATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
THIETHYLPERAZINE MALEATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
THYROXINE	0 .	2 (0.4%)	2 (0.3%)
TIEMONIUM IODIDE	0 .	2 (0.4%)	2 (0.3%)
TIMOLOL	2 (0.8%)	0 .	2 (0.3%)
TIMOLOL MALEATE	0 .	2 (0.4%)	2 (0.3%)
TITANIUM DIOXIDE	0 .	2 (0.4%)	2 (0.3%)
TOLPERISONE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)
TRANEXAMIC ACID	0 .	2 (0.4%)	2 (0.3%)
TRAZODONE	1 (0.4%)	1 (0.2%)	2 (0.3%)
TRAZODONE HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
TROPICAMIDE	2 (0.8%)	0 .	2 (0.3%)
TROSPIMUM CHLORIDE	2 (0.8%)	0 .	2 (0.3%)
UNKNOWN MEDICATION	0 .	2 (0.4%)	2 (0.3%)
URTICA EXTRACT	0 .	2 (0.4%)	2 (0.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

SB 207499

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
XYLOMETAZOLINE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)
YEAST DRIED	0 .	2 (0.4%)	2 (0.3%)
ZANAMIVIR	0 .	2 (0.4%)	2 (0.3%)
ZOLMITRIPTAN	1 (0.4%)	1 (0.2%)	2 (0.3%)
ACAMPROSATE	0 .	1 (0.2%)	1 (0.1%)
ACEPROMAZINE	0 .	1 (0.2%)	1 (0.1%)
ACEPROMETAZINE	0 .	1 (0.2%)	1 (0.1%)
ACETYL-GLUCOSAMINE	0 .	1 (0.2%)	1 (0.1%)
ACETYLSALICYLATE CALCIUM	0 .	1 (0.2%)	1 (0.1%)
ACONITE TINCTURE	0 .	1 (0.2%)	1 (0.1%)
ADENOSINE PHOSPHATE, SODIUM SALT	0 .	1 (0.2%)	1 (0.1%)
ADENOSINE TRIPHOSPHATE	0 .	1 (0.2%)	1 (0.1%)
ADENOSINE TRIPHOSPHATE, DISODIUM SALT	1 (0.4%)	0 .	1 (0.1%)
ALBUMEN	0 .	1 (0.2%)	1 (0.1%)
ALFACALCIDOL	1 (0.4%)	0 .	1 (0.1%)
ALLERGENIC EXTRACT, NOS	0 .	1 (0.2%)	1 (0.1%)
ALPROSTADIL	0 .	1 (0.2%)	1 (0.1%)
AMANTADINE SULFATE	0 .	1 (0.2%)	1 (0.1%)
AMFEBUTAMONE HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)
AMINEPTINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
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4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
AMINO ACIDS NOS	0 .	1 (0.2%)	1 (0.1%)
AMINOACRIDINE	0 .	1 (0.2%)	1 (0.1%)
AMINOBENZOIC ACID	0 .	1 (0.2%)	1 (0.1%)
AMINOCAPROIC ACID	1 (0.4%)	0 .	1 (0.1%)
AMINOHYDROXYPROPYLIDENEDIPHOSPHONATE DISODIUM	1 (0.4%)	0 .	1 (0.1%)
AMINOPENTAMIDE	1 (0.4%)	0 .	1 (0.1%)
AMINOSALICYLIC ACID	0 .	1 (0.2%)	1 (0.1%)
AMISULPRIDE	1 (0.4%)	0 .	1 (0.1%)
AMPICILLIN	0 .	1 (0.2%)	1 (0.1%)
AMPICILLIN BENZATHINE	0 .	1 (0.2%)	1 (0.1%)
AMYLASE	1 (0.4%)	0 .	1 (0.1%)
ANALGESICS	0 .	1 (0.2%)	1 (0.1%)
ANESTHESIA, NOS	1 (0.4%)	0 .	1 (0.1%)
ANETHOLE	0 .	1 (0.2%)	1 (0.1%)
ANISATED SPIRIT OF AMMONIA	0 .	1 (0.2%)	1 (0.1%)
ANTAZOLINE SULFATE	0 .	1 (0.2%)	1 (0.1%)
ANTIINFLAMMATORY NOS	0 .	1 (0.2%)	1 (0.1%)
ARACHIS OIL	1 (0.4%)	0 .	1 (0.1%)
ARGININE ASPARTATE	0 .	1 (0.2%)	1 (0.1%)
ASPARTATE POTASSIUM	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
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TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
ASPARTIC ACID	0 .	1 (0.2%)	1 (0.1%)
ATRACURIUM BESILATE	0 .	1 (0.2%)	1 (0.1%)
AZELASTINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
BACITRACIN ZINC	0 .	1 (0.2%)	1 (0.1%)
BAMBUTEROL HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)
BCG VACCINE	1 (0.4%)	0 .	1 (0.1%)
BELLADONNA TINCTURE	0 .	1 (0.2%)	1 (0.1%)
BEMETIZIDE	0 .	1 (0.2%)	1 (0.1%)
BENACTYZINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
BENFLUOREX	1 (0.4%)	0 .	1 (0.1%)
BENFLUOREX HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)
BENFOTIAMINE	0 .	1 (0.2%)	1 (0.1%)
BENSERAZIDE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
BENZATHINE BENZYL PENICILLIN	0 .	1 (0.2%)	1 (0.1%)
BENZODODECINIUM BROMIDE	1 (0.4%)	0 .	1 (0.1%)
BENZOYL PEROXIDE	0 .	1 (0.2%)	1 (0.1%)
BENZYDAMINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
BENZYL BENZOATE	1 (0.4%)	0 .	1 (0.1%)
BENZYL-P-PHENOL	1 (0.4%)	0 .	1 (0.1%)
BEPRIDIL HYDROCHLORIDE MONOHYDRATE	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
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TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
BETACAROTENE	0 .	1 (0.2%)	1 (0.1%)
BETAHISTINE MALEATE	0 .	1 (0.2%)	1 (0.1%)
BIBROCATHOL	0 .	1 (0.2%)	1 (0.1%)
BICALUTAMIDE	1 (0.4%)	0 .	1 (0.1%)
BICLOTYMOL	1 (0.4%)	0 .	1 (0.1%)
BIFIDOBACTERIUM BIFIDUM	0 .	1 (0.2%)	1 (0.1%)
BIOFLAVONOIDS	1 (0.4%)	0 .	1 (0.1%)
BIPERIDEN HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
BISMUTH CAMPHOCARBONATE	0 .	1 (0.2%)	1 (0.1%)
BISMUTH SUBCARBONATE	1 (0.4%)	0 .	1 (0.1%)
BORIC ACID	0 .	1 (0.2%)	1 (0.1%)
BROMHEXINE	1 (0.4%)	0 .	1 (0.1%)
BUSPIRONE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
BUTACAINE SULPHATE	1 (0.4%)	0 .	1 (0.1%)
BUTETAMATE CITRATE	0 .	1 (0.2%)	1 (0.1%)
BUTYLATED HYDROXYANISOLE	0 .	1 (0.2%)	1 (0.1%)
BUTYLATED HYDROXYTOLUENE	0 .	1 (0.2%)	1 (0.1%)
CAJEPUTOL OIL	1 (0.4%)	0 .	1 (0.1%)
CALCIPOTRIOL	0 .	1 (0.2%)	1 (0.1%)
CALCITONIN	1 (0.4%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
-----	-----	-----	-----
CALCITONIN, SALMON	0 .	1 (0.2%)	1 (0.1%)
CALCIUM GLUBIONATE	1 (0.4%)	0 .	1 (0.1%)
CALCIUM GLUCEPTATE	1 (0.4%)	0 .	1 (0.1%)
CALCIUM GLUCONATE	0 .	1 (0.2%)	1 (0.1%)
CALCIUM PIDOLATE	0 .	1 (0.2%)	1 (0.1%)
CALCIUM POLYSTYRENE SULFONATE	0 .	1 (0.2%)	1 (0.1%)
CAMPHOR MONOBROMIDE	0 .	1 (0.2%)	1 (0.1%)
CAPSAICIN	0 .	1 (0.2%)	1 (0.1%)
CARBACHOL	0 .	1 (0.2%)	1 (0.1%)
CARBIDOPA	0 .	1 (0.2%)	1 (0.1%)
CARTEOLOL HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)
CEDAR OIL	1 (0.4%)	0 .	1 (0.1%)
CEFAPIRIN SODIUM	1 (0.4%)	0 .	1 (0.1%)
CEFEPIM	0 .	1 (0.2%)	1 (0.1%)
CEFOTAXIME	1 (0.4%)	0 .	1 (0.1%)
CEFOTIAM	0 .	1 (0.2%)	1 (0.1%)
CEFPiROME SULFATE	0 .	1 (0.2%)	1 (0.1%)
CEFPiROZIL MONOHYDRATE	0 .	1 (0.2%)	1 (0.1%)
CEFRADINE	0 .	1 (0.2%)	1 (0.1%)
CEFTAZIDIME	1 (0.4%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
CETOMACROGOL	0 .	1 (0.2%)	1 (0.1%)
CETOSTEARYL ALCOHOL	0 .	1 (0.2%)	1 (0.1%)
CETYLPYRIDINIUM CHLORIDE	0 .	1 (0.2%)	1 (0.1%)
CETYLPYRIDINIUM CHLORIDE	0 .	1 (0.2%)	1 (0.1%)
CHAMOMILE	0 .	1 (0.2%)	1 (0.1%)
CHAMOMILE OIL	0 .	1 (0.2%)	1 (0.1%)
CHINOFORM	1 (0.4%)	0 .	1 (0.1%)
CHLORHEXIDINE DIACETATE	1 (0.4%)	0 .	1 (0.1%)
CHLORINATED LIME AND BORIC ACID SOLUTION	0 .	1 (0.2%)	1 (0.1%)
CHLORMADINONE ACETATE	0 .	1 (0.2%)	1 (0.1%)
CHLORMETHINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
CHLORMEZANONE	0 .	1 (0.2%)	1 (0.1%)
CHLOROFORM AND MORPHINE TINCTURE	1 (0.4%)	0 .	1 (0.1%)
CHLOROPHYLL	1 (0.4%)	0 .	1 (0.1%)
CHLOROQUINE SULFATE	0 .	1 (0.2%)	1 (0.1%)
CHLORPHENAMINE	1 (0.4%)	0 .	1 (0.1%)
CHLORPROPAMIDE	0 .	1 (0.2%)	1 (0.1%)
CHOLINE BITARTRATE	0 .	1 (0.2%)	1 (0.1%)
CHOLINE THEOPHYLLINATE	0 .	1 (0.2%)	1 (0.1%)
CHONDROITIN SULFATE SODIUM	1 (0.4%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
CICLOPIROX	0 .	1 (0.2%)	1 (0.1%)
CIMICIFUGA	0 .	1 (0.2%)	1 (0.1%)
CINITAPRIDE TARTRATE	1 (0.4%)	0 .	1 (0.1%)
CIPROFIBRATE	0 .	1 (0.2%)	1 (0.1%)
CLAVULANATE	0 .	1 (0.2%)	1 (0.1%)
CLEMASTINE	0 .	1 (0.2%)	1 (0.1%)
CLEMIZOLE UNDECYLENATE	1 (0.4%)	0 .	1 (0.1%)
CLINDAMYCIN	0 .	1 (0.2%)	1 (0.1%)
CLIOQUINOL	1 (0.4%)	0 .	1 (0.1%)
CLOBUTINOL HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
CLOCINIZINE	1 (0.4%)	0 .	1 (0.1%)
CLOFOCTOL	1 (0.4%)	0 .	1 (0.1%)
CLOMETOCILLIN POTASSIUM	1 (0.4%)	0 .	1 (0.1%)
CLOPREDNOL	0 .	1 (0.2%)	1 (0.1%)
CLOTIAZEPAM	1 (0.4%)	0 .	1 (0.1%)
COAL TAR SOLUTION	0 .	1 (0.2%)	1 (0.1%)
COUGH COLD PREPARATIONS NOS	0 .	1 (0.2%)	1 (0.1%)
CREATININE SULFATE	1 (0.4%)	0 .	1 (0.1%)
CROTAMITON	0 .	1 (0.2%)	1 (0.1%)
CUCURBITA PEPO	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
CYAMEMAZINE	0 .	1 (0.2%)	1 (0.1%)
CYPROHEPTADINE HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)
CYPROTERONE ACETATE	1 (0.4%)	0 .	1 (0.1%)
DEOXYRIBONUCLEIC ACID	0 .	1 (0.2%)	1 (0.1%)
DESONIDE	1 (0.4%)	0 .	1 (0.1%)
DESOXIMETASONE	1 (0.4%)	0 .	1 (0.1%)
DEXAMETHASONE ISONICOTINATE	0 .	1 (0.2%)	1 (0.1%)
DEXAMETHASONE SODIUM METASULFOBENZOATE	0 .	1 (0.2%)	1 (0.1%)
DEXCHLORPHENIRAMINE	0 .	1 (0.2%)	1 (0.1%)
DEXPANTHENOL	1 (0.4%)	0 .	1 (0.1%)
DEXTRAN 40	0 .	1 (0.2%)	1 (0.1%)
DEXTROSE PARENTERALS	0 .	1 (0.2%)	1 (0.1%)
DIASTASE	0 .	1 (0.2%)	1 (0.1%)
DICLOFENAC EPOLAMINE	1 (0.4%)	0 .	1 (0.1%)
DICYCLOVERINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
DIENESTROL	1 (0.4%)	0 .	1 (0.1%)
DIETHANOLAMINE	0 .	1 (0.2%)	1 (0.1%)
DIFEBARBAMATE	0 .	1 (0.2%)	1 (0.1%)
DIGITOXIN	0 .	1 (0.2%)	1 (0.1%)
DIHYDROCODEINE	1 (0.4%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
DIHYDROERGOCRYPTINE MESILATE	1 (0.4%)	0 .	1 (0.1%)
DIMEMORFAN PHOSPHATE	1 (0.4%)	0 .	1 (0.1%)
DIMENHYDRINATE	1 (0.4%)	0 .	1 (0.1%)
DIMETINDENE MALEATE	1 (0.4%)	0 .	1 (0.1%)
DISODIUM METHANEARSONATE	1 (0.4%)	0 .	1 (0.1%)
DISOPYRAMIDE	1 (0.4%)	0 .	1 (0.1%)
DISOPYRAMIDE PHOSPHATE	0 .	1 (0.2%)	1 (0.1%)
DITAZOLE	0 .	1 (0.2%)	1 (0.1%)
DOXYCYCLINE CALCIUM	1 (0.4%)	0 .	1 (0.1%)
DOXYCYCLINE MONOHYDRATE	0 .	1 (0.2%)	1 (0.1%)
DOXYLAMINE	0 .	1 (0.2%)	1 (0.1%)
DOXYLAMINE SUCCINATE	0 .	1 (0.2%)	1 (0.1%)
ELDER BLOSSOM	0 .	1 (0.2%)	1 (0.1%)
ELECTROLYTES NOS	1 (0.4%)	0 .	1 (0.1%)
EMOLLIENT BASE NOS	0 .	1 (0.2%)	1 (0.1%)
ENOXACIN	0 .	1 (0.2%)	1 (0.1%)
ENOXAPARIN SODIUM	0 .	1 (0.2%)	1 (0.1%)
ENTEROCOCCUS FAECIUM	0 .	1 (0.2%)	1 (0.1%)
EPHEDRINE	0 .	1 (0.2%)	1 (0.1%)
EPHEDRINE SULFATE	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
EPRAZINONE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
EPROSARTAN	0 .	1 (0.2%)	1 (0.1%)
ERGOCALCIFEROL	1 (0.4%)	0 .	1 (0.1%)
ERGOTAMINE TARTRATE	0 .	1 (0.2%)	1 (0.1%)
ERYSIMUM EXTRACT	0 .	1 (0.2%)	1 (0.1%)
ESCHERICHIA COLI	0 .	1 (0.2%)	1 (0.1%)
ESCIN	1 (0.4%)	0 .	1 (0.1%)
ESSENTIAL OILS NOS	0 .	1 (0.2%)	1 (0.1%)
ESTROGEN NOS	0 .	1 (0.2%)	1 (0.1%)
ETHANOL	0 .	1 (0.2%)	1 (0.1%)
ETHENZAMIDE	0 .	1 (0.2%)	1 (0.1%)
ETHYL CHLORIDE	1 (0.4%)	0 .	1 (0.1%)
ETHYL NICOTINATE	1 (0.4%)	0 .	1 (0.1%)
ETHYLMORPHINE	0 .	1 (0.2%)	1 (0.1%)
ETHYLMORPHINE CAMSILATE	0 .	1 (0.2%)	1 (0.1%)
ETIDRONATE DISODIUM	1 (0.4%)	0 .	1 (0.1%)
ETIDRONIC ACID	0 .	1 (0.2%)	1 (0.1%)
ETOFYLLINE	0 .	1 (0.2%)	1 (0.1%)
EUGENOL	0 .	1 (0.2%)	1 (0.1%)
EUPHORBIA	1 (0.4%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040
INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

SB 207499

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
EUPHORBIA LIQUID EXTRACT	1 (0.4%)	0 .	1 (0.1%)
EXPECTORANTS NOS	0 .	1 (0.2%)	1 (0.1%)
FAMCICLOVIR	0 .	1 (0.2%)	1 (0.1%)
FENDILINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
FENOPROFEN CALCIUM	0 .	1 (0.2%)	1 (0.1%)
FENOTEROL	0 .	1 (0.2%)	1 (0.1%)
FENTICONAZOLE NITRATE	0 .	1 (0.2%)	1 (0.1%)
FERROUS FUMARATE	1 (0.4%)	0 .	1 (0.1%)
FINASTERIDE	1 (0.4%)	0 .	1 (0.1%)
FLECAINIDE	0 .	1 (0.2%)	1 (0.1%)
FLUMETASONE PIVALATE	1 (0.4%)	0 .	1 (0.1%)
FLUOCORTOLONE	1 (0.4%)	0 .	1 (0.1%)
FLUOCORTOLONE CAPROATE	1 (0.4%)	0 .	1 (0.1%)
FLUOXETINE HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)
FLUPENTIXOL DIHYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
FOSFOMYCIN	0 .	1 (0.2%)	1 (0.1%)
FRANGULA EXTRACT	1 (0.4%)	0 .	1 (0.1%)
FRANGULIN	1 (0.4%)	0 .	1 (0.1%)
GABAPENTIN	0 .	1 (0.2%)	1 (0.1%)
GALLOPAMIL HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
GLUCOSAMINE SULFATE	0 .	1 (0.2%)	1 (0.1%)
GLUCURONAMIDE	0 .	1 (0.2%)	1 (0.1%)
GLUTATHIONE	0 .	1 (0.2%)	1 (0.1%)
GLYCOL SALICYLATE	0 .	1 (0.2%)	1 (0.1%)
GLYCOSAMINOGLYCAN POLYSULFATE	0 .	1 (0.2%)	1 (0.1%)
GRAPE SEED	1 (0.4%)	0 .	1 (0.1%)
GREPAFLOXACIN HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)
GRINDELIA	0 .	1 (0.2%)	1 (0.1%)
GRINDELIA LIQUID EXTRACT	0 .	1 (0.2%)	1 (0.1%)
GRISEOFULVIN	0 .	1 (0.2%)	1 (0.1%)
GUANABENZ ACETATE	1 (0.4%)	0 .	1 (0.1%)
HEMATOPORPHYRIN	0 .	1 (0.2%)	1 (0.1%)
HEXACHLOROPHENE	1 (0.4%)	0 .	1 (0.1%)
HEXYL NICOTINATE	1 (0.4%)	0 .	1 (0.1%)
HEXYLRESORCINOL	0 .	1 (0.2%)	1 (0.1%)
HIDROSMIN	0 .	1 (0.2%)	1 (0.1%)
HISTAMINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
HYALURONIDASE	0 .	1 (0.2%)	1 (0.1%)
HYDROCORTISONE SODIUM SUCCINATE	0 .	1 (0.2%)	1 (0.1%)
HYDROXYCHLOROQUINE SULFATE	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
HYDROXYETHYL THEOPHYLLINE	0 .	1 (0.2%)	1 (0.1%)
HYPERTONIC SEA WATER SOLUTION	1 (0.4%)	0 .	1 (0.1%)
ICHTHAMMOL	0 .	1 (0.2%)	1 (0.1%)
IMIDUREA	0 .	1 (0.2%)	1 (0.1%)
INOSITOL	0 .	1 (0.2%)	1 (0.1%)
INSULIN PORCINE BASE	0 .	1 (0.2%)	1 (0.1%)
INTRINSIC FACTOR	1 (0.4%)	0 .	1 (0.1%)
IODINE (131 I)	0 .	1 (0.2%)	1 (0.1%)
IPRATROPIUM	0 .	1 (0.2%)	1 (0.1%)
ISOPROMETHAZINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
ISPAGHULA HUSKS	0 .	1 (0.2%)	1 (0.1%)
JOSAMYCIN	0 .	1 (0.2%)	1 (0.1%)
KANAMYCIN SULFATE	1 (0.4%)	0 .	1 (0.1%)
KAOLIN	1 (0.4%)	0 .	1 (0.1%)
KETOBEMIDONE HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)
KETOROLAC	1 (0.4%)	0 .	1 (0.1%)
KETOTIFEN FUMARATE	1 (0.4%)	0 .	1 (0.1%)
LACTOBACILLUS ACIDOPHILUS	0 .	1 (0.2%)	1 (0.1%)
LACTOBACILLUS LACTIS	1 (0.4%)	0 .	1 (0.1%)
LACTOSE	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
LACTUCA EXTRACT	1 (0.4%)	0 .	1 (0.1%)
LACTUCA SYRUP	1 (0.4%)	0 .	1 (0.1%)
LANOLIN	0 .	1 (0.2%)	1 (0.1%)
LECITHIN	0 .	1 (0.2%)	1 (0.1%)
LEUCOCIANIDOL	1 (0.4%)	0 .	1 (0.1%)
LEVOBUNOLOL HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
LEVODOPA	0 .	1 (0.2%)	1 (0.1%)
LEVODROPROPIZINE	0 .	1 (0.2%)	1 (0.1%)
LEVOGLUTAMIDE	1 (0.4%)	0 .	1 (0.1%)
LEVOMEPRMAZINE MALEATE	1 (0.4%)	0 .	1 (0.1%)
LINCOMYCIN HYDROCHLORIDE MONOHYDRATE	0 .	1 (0.2%)	1 (0.1%)
LINDANE	1 (0.4%)	0 .	1 (0.1%)
LIPOPHILER EXTRACT	0 .	1 (0.2%)	1 (0.1%)
LIVER EXTRACTS	0 .	1 (0.2%)	1 (0.1%)
LOFEPRAMINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
LOMEFLOXACIN	1 (0.4%)	0 .	1 (0.1%)
LORACARBEF	0 .	1 (0.2%)	1 (0.1%)
LORNOXICAM	1 (0.4%)	0 .	1 (0.1%)
LOSARTAN	1 (0.4%)	0 .	1 (0.1%)
LYCOPUS EUROPAEUS	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040
INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
MAGALDRATE	1 (0.4%)	0 .	1 (0.1%)
MAGNESIUM ASCORBATE	0 .	1 (0.2%)	1 (0.1%)
MAGNESIUM CHLORIDE	1 (0.4%)	0 .	1 (0.1%)
MAGNESIUM GLUCONATE	1 (0.4%)	0 .	1 (0.1%)
MAGNESIUM GLYCEROPHOSPHATE	1 (0.4%)	0 .	1 (0.1%)
MAGNESIUM LEVULINATE	1 (0.4%)	0 .	1 (0.1%)
MAGNESIUM PIDOLATE	0 .	1 (0.2%)	1 (0.1%)
MAGNESIUM SALT	0 .	1 (0.2%)	1 (0.1%)
MAGNESIUM SPAGLUMINATE	0 .	1 (0.2%)	1 (0.1%)
MAPROTILINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
MARRUBE EXTRACT	0 .	1 (0.2%)	1 (0.1%)
MEDROGESTONE	1 (0.4%)	0 .	1 (0.1%)
MEDROXYPROGESTERONE ACETATE	1 (0.4%)	0 .	1 (0.1%)
MELISSA EXTRACT	0 .	1 (0.2%)	1 (0.1%)
MENADIONE	1 (0.4%)	0 .	1 (0.1%)
MEQUITAZINE	0 .	1 (0.2%)	1 (0.1%)
METHENAMINE	0 .	1 (0.2%)	1 (0.1%)
METHYLCLOTHIAZIDE	1 (0.4%)	0 .	1 (0.1%)
METHYL NICOTINATE	0 .	1 (0.2%)	1 (0.1%)
METHYL SALICYLATE	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
METHYLDOPA	0 .	1 (0.2%)	1 (0.1%)
METHYLPARABEN	0 .	1 (0.2%)	1 (0.1%)
METHYLTHIONINIUM CHLORIDE	0 .	1 (0.2%)	1 (0.1%)
METILDIGOXIN	0 .	1 (0.2%)	1 (0.1%)
METOPIMAZINE	1 (0.4%)	0 .	1 (0.1%)
MIANSERIN	0 .	1 (0.2%)	1 (0.1%)
MIDAZOLAM	1 (0.4%)	0 .	1 (0.1%)
MIDECAMYCIN	0 .	1 (0.2%)	1 (0.1%)
MINERAL OIL, LIGHT	0 .	1 (0.2%)	1 (0.1%)
MINOCYCLINE	1 (0.4%)	0 .	1 (0.1%)
MINOCYCLINE HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)
MIOKAMYCIN	0 .	1 (0.2%)	1 (0.1%)
MIRTAZAPINE	1 (0.4%)	0 .	1 (0.1%)
MISTLETOE EXTRACT	0 .	1 (0.2%)	1 (0.1%)
MOCLOBEMIDE	1 (0.4%)	0 .	1 (0.1%)
MOMETASONE	0 .	1 (0.2%)	1 (0.1%)
MUCOPOLYSACCHARIDES	1 (0.4%)	0 .	1 (0.1%)
MULTIMINERALS	1 (0.4%)	0 .	1 (0.1%)
MYRTECAINE	0 .	1 (0.2%)	1 (0.1%)
MYRTOL	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
N,N-DIMETHYL-3,3-DIPHENYL-1-METHYLALLYLAMINE HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)
NADOLOL	0 .	1 (0.2%)	1 (0.1%)
NEOMYCIN	1 (0.4%)	0 .	1 (0.1%)
NICERGOLINE	0 .	1 (0.2%)	1 (0.1%)
NITROFURANTOIN	1 (0.4%)	0 .	1 (0.1%)
NORDAZEPAM	0 .	1 (0.2%)	1 (0.1%)
NORETHISTERONE	1 (0.4%)	0 .	1 (0.1%)
NOSCAPINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
NSAID, NOS	0 .	1 (0.2%)	1 (0.1%)
NUCLEOTIDES NOS	0 .	1 (0.2%)	1 (0.1%)
NUTMEG OIL	1 (0.4%)	0 .	1 (0.1%)
ONDANSETRON HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
OPIPRAMOL HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
OPIUM TINCTURE	0 .	1 (0.2%)	1 (0.1%)
ORANGE COLOURING	0 .	1 (0.2%)	1 (0.1%)
ORANGE ESSENCE	0 .	1 (0.2%)	1 (0.1%)
ORLISTAT	1 (0.4%)	0 .	1 (0.1%)
ORNITHINE OXOGLURATE	1 (0.4%)	0 .	1 (0.1%)
OROTIC ACID	0 .	1 (0.2%)	1 (0.1%)
OTILONIUM BROMIDE	1 (0.4%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
OXACEPROL	1 (0.4%)	0 .	1 (0.1%)
OXOMEMAZINE	0 .	1 (0.2%)	1 (0.1%)
OXYBUTYNIN HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
OXYFEDRINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
PANTHENOL	0 .	1 (0.2%)	1 (0.1%)
PARADICHLOROBENZENE	1 (0.4%)	0 .	1 (0.1%)
PARAHYDROXYCINNAMIC ACID	0 .	1 (0.2%)	1 (0.1%)
PEMOLINE	1 (0.4%)	0 .	1 (0.1%)
PENCICLOVIR	0 .	1 (0.2%)	1 (0.1%)
PENTETRAZOL	0 .	1 (0.2%)	1 (0.1%)
PENTOBARBITAL	1 (0.4%)	0 .	1 (0.1%)
PEPSIN	0 .	1 (0.2%)	1 (0.1%)
PETHIDINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
PHENACETIN	0 .	1 (0.2%)	1 (0.1%)
PHENINDIONE	0 .	1 (0.2%)	1 (0.1%)
PHENIRAMINE AMINOSALICYLATE	0 .	1 (0.2%)	1 (0.1%)
PHENIRAMINE MALEATE	0 .	1 (0.2%)	1 (0.1%)
PHENOBARBITAL CALCIUM	0 .	1 (0.2%)	1 (0.1%)
PHENOXYMETHYLPENICILLIN HYDRABAMINE	0 .	1 (0.2%)	1 (0.1%)
PHENYTOIN	1 (0.4%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
PHYTOMENADIONE	1 (0.4%)	0 .	1 (0.1%)
PIKETOPROFEN	1 (0.4%)	0 .	1 (0.1%)
PILOCARPINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
PIMPINELLA ROOT	0 .	1 (0.2%)	1 (0.1%)
PINAVERIUM BROMIDE	0 .	1 (0.2%)	1 (0.1%)
PIOGLITAZONE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
PIRACETAM	1 (0.4%)	0 .	1 (0.1%)
PIRIBEDIL	1 (0.4%)	0 .	1 (0.1%)
PITOFENONE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
PIVMECILLINAM	0 .	1 (0.2%)	1 (0.1%)
PIVMECILLINAM HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
POLIOMYELITIS VACCINE INACTIVATED	0 .	1 (0.2%)	1 (0.1%)
POLYGALA AMARA TINCTURE	0 .	1 (0.2%)	1 (0.1%)
POLYGALA SENEGA	1 (0.4%)	0 .	1 (0.1%)
POLYSORBATE 80	1 (0.4%)	0 .	1 (0.1%)
POPULUS EXTRACT	0 .	1 (0.2%)	1 (0.1%)
POPULUS TREMULA	0 .	1 (0.2%)	1 (0.1%)
POTASSIUM IODIDE	0 .	1 (0.2%)	1 (0.1%)
PRASTERONE	1 (0.4%)	0 .	1 (0.1%)
PREDNICARBATE	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
PREDNISOLONE CAPROATE	1 (0.4%)	0 .	1 (0.1%)
PREDNISOLONE-FENOXAZOLINE COMPOUND	0 .	1 (0.2%)	1 (0.1%)
PRIMULA RHIZOME	0 .	1 (0.2%)	1 (0.1%)
PROCAINE	0 .	1 (0.2%)	1 (0.1%)
PROGESTERONE	0 .	1 (0.2%)	1 (0.1%)
PROGUANIL HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
PROMETHAZINE	0 .	1 (0.2%)	1 (0.1%)
PROMETHAZINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
PROPANTHELINE BROMIDE	0 .	1 (0.2%)	1 (0.1%)
PROTEIN HYDROLYSATE	1 (0.4%)	0 .	1 (0.1%)
QUEBRACHO BARK	0 .	1 (0.2%)	1 (0.1%)
RABEPRAZOLE SODIUM	1 (0.4%)	0 .	1 (0.1%)
RAUWOLFIA	0 .	1 (0.2%)	1 (0.1%)
RESCINNAMINE	1 (0.4%)	0 .	1 (0.1%)
RESERPINE	0 .	1 (0.2%)	1 (0.1%)
RETINOL ACETATE	0 .	1 (0.2%)	1 (0.1%)
RISEDRONIC ACID MONOSODIUM SALT	0 .	1 (0.2%)	1 (0.1%)
RITIOMETAN	0 .	1 (0.2%)	1 (0.1%)
ROCURONIUM	0 .	1 (0.2%)	1 (0.1%)
ROSEMARY OIL	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

SB 207499

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
ROSIGLITAZONE	0 .	1 (0.2%)	1 (0.1%)
ROXATIDINE HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)
RUSCOGENIN	0 .	1 (0.2%)	1 (0.1%)
RUSCUS ACULEATUS RHIZOME	1 (0.4%)	0 .	1 (0.1%)
SACCHAROMYCES CEREVISIAE	0 .	1 (0.2%)	1 (0.1%)
SALICYLATE SODIUM	0 .	1 (0.2%)	1 (0.1%)
SCOPARIUM	0 .	1 (0.2%)	1 (0.1%)
SELENIUM	0 .	1 (0.2%)	1 (0.1%)
SENNA FRUIT	1 (0.4%)	0 .	1 (0.1%)
SERTRALINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
SEVOFLURANE	0 .	1 (0.2%)	1 (0.1%)
SIBUTRAMINE	0 .	1 (0.2%)	1 (0.1%)
SILICON DIOXIDE, COLLOIDAL	0 .	1 (0.2%)	1 (0.1%)
SITOSTEROLS	1 (0.4%)	0 .	1 (0.1%)
SODIUM AUROTHIOMALATE	1 (0.4%)	0 .	1 (0.1%)
SODIUM BORATE	0 .	1 (0.2%)	1 (0.1%)
SODIUM BROMIDE	0 .	1 (0.2%)	1 (0.1%)
SODIUM FLUORIDE	0 .	1 (0.2%)	1 (0.1%)
SODIUM LACTATE	1 (0.4%)	0 .	1 (0.1%)
SODIUM MONOMETHYLTRISILANOL ORTHOHYDROXY-BENZOATE	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040
INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
SODIUM PHOSPHATE	0 .	1 (0.2%)	1 (0.1%)
SODIUM PICOSULFATE	0 .	1 (0.2%)	1 (0.1%)
SODIUM PROPYLPARABEN	0 .	1 (0.2%)	1 (0.1%)
SODIUM SULFATE	0 .	1 (0.2%)	1 (0.1%)
SODIUM SULFATE ANHYDROUS	1 (0.4%)	0 .	1 (0.1%)
SOLIDAGO	0 .	1 (0.2%)	1 (0.1%)
SORREL GARDEN HERB	0 .	1 (0.2%)	1 (0.1%)
SOTALOL	1 (0.4%)	0 .	1 (0.1%)
SPINAL ANESTHESIA	0 .	1 (0.2%)	1 (0.1%)
SPIRAMYCIN	0 .	1 (0.2%)	1 (0.1%)
SPIRAMYCIN 2	0 .	1 (0.2%)	1 (0.1%)
SQUILL EXTRACT	1 (0.4%)	0 .	1 (0.1%)
SQUILL SYRUP COMPOUND	1 (0.4%)	0 .	1 (0.1%)
STREPTOCOCCUS FAECALIS	0 .	1 (0.2%)	1 (0.1%)
STREPTODORNASE	1 (0.4%)	0 .	1 (0.1%)
STREPTOKINASE	1 (0.4%)	0 .	1 (0.1%)
SUFENTANIL CITRATE	0 .	1 (0.2%)	1 (0.1%)
SULBACTAM	0 .	1 (0.2%)	1 (0.1%)
SULFADIAZINE SILVER	0 .	1 (0.2%)	1 (0.1%)
SULFAMETHIZOLE	1 (0.4%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
SULFASALAZINE	1 (0.4%)	0 .	1 (0.1%)
SULFATE	1 (0.4%)	0 .	1 (0.1%)
SULFUR	0 .	1 (0.2%)	1 (0.1%)
SULPHANILAMIDE	1 (0.4%)	0 .	1 (0.1%)
SUMATRIPTAN	0 .	1 (0.2%)	1 (0.1%)
TAMOXIFEN	1 (0.4%)	0 .	1 (0.1%)
TAMSULOSIN	1 (0.4%)	0 .	1 (0.1%)
TARTARIC ACID	0 .	1 (0.2%)	1 (0.1%)
TERAZOSIN	0 .	1 (0.2%)	1 (0.1%)
TERBINAFINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
TERPINEOL	0 .	1 (0.2%)	1 (0.1%)
TESTOSTERONE ENANTATE	1 (0.4%)	0 .	1 (0.1%)
TETANUS ANTITOXIN	1 (0.4%)	0 .	1 (0.1%)
TETRACYCLINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
THIOCTIC ACID	0 .	1 (0.2%)	1 (0.1%)
THIORIDAZINE	1 (0.4%)	0 .	1 (0.1%)
THURFYL SALICYLATE	1 (0.4%)	0 .	1 (0.1%)
THYME EXTRACT	0 .	1 (0.2%)	1 (0.1%)
THYME OIL	0 .	1 (0.2%)	1 (0.1%)
TICARCILLIN DISODIUM	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
TICLOPIDINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
TISSUE PLASMINOGEN ACTIVATOR	1 (0.4%)	0 .	1 (0.1%)
TOBRAMYCIN SULFATE	0 .	1 (0.2%)	1 (0.1%)
TOLBUTAMIDE	0 .	1 (0.2%)	1 (0.1%)
TOLFENAMIC ACID	1 (0.4%)	0 .	1 (0.1%)
TOLNAFTATE	1 (0.4%)	0 .	1 (0.1%)
TOPICAL STEROID NOS	0 .	1 (0.2%)	1 (0.1%)
TRAMAZOLINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
TRAPIDIL	0 .	1 (0.2%)	1 (0.1%)
TRETINOIN	1 (0.4%)	0 .	1 (0.1%)
TRIENTINE	0 .	1 (0.2%)	1 (0.1%)
TRIMEBUTINE	0 .	1 (0.2%)	1 (0.1%)
TRIMEBUTINE MALEATE	0 .	1 (0.2%)	1 (0.1%)
TRIMIPRAMINE	0 .	1 (0.2%)	1 (0.1%)
TRIMIPRAMINE MALEATE	0 .	1 (0.2%)	1 (0.1%)
UBIDECARENONE	1 (0.4%)	0 .	1 (0.1%)
UNDECYLENIC ACID	1 (0.4%)	0 .	1 (0.1%)
URAPIDIL	0 .	1 (0.2%)	1 (0.1%)
URIDINE TRIPHOSPHATE SODIUM	0 .	1 (0.2%)	1 (0.1%)
UROKINASE	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10B

SUMMARY OF CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
VALACYCLOVIR HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
VALERIAN TINCTURE	0 .	1 (0.2%)	1 (0.1%)
VALPROATE SODIUM	0 .	1 (0.2%)	1 (0.1%)
VERALIPRIDE	1 (0.4%)	0 .	1 (0.1%)
VERATROLE	0 .	1 (0.2%)	1 (0.1%)
VILOXAZINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
VINCAMINE	0 .	1 (0.2%)	1 (0.1%)
VIRGAUREA HERB	0 .	1 (0.2%)	1 (0.1%)
VITIS VINIFERA	0 .	1 (0.2%)	1 (0.1%)
XIPAMIDE	1 (0.4%)	0 .	1 (0.1%)
ZIPEPROL DIHYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)
ZOLPIDEM	1 (0.4%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10C

SUMMARY OF CONCOMITANT MEDICATIONS GIVEN FOR EXACERBATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
TOTAL	146 (60.1%)	310 (64.6%)	456 (63.1%)
AMOXICILLIN TRIHYDRATE	53 (21.8%)	112 (23.3%)	165 (22.8%)
CLAVULANIC ACID	36 (14.8%)	86 (17.9%)	122 (16.9%)
ACETYLCYSTEINE	31 (12.8%)	55 (11.5%)	86 (11.9%)
PREDNISOLONE	30 (12.3%)	56 (11.7%)	86 (11.9%)
PARACETAMOL	25 (10.3%)	51 (10.6%)	76 (10.5%)
AZITHROMYCIN	32 (13.2%)	43 (9.0%)	75 (10.4%)
PREDNISONE	23 (9.5%)	46 (9.6%)	69 (9.5%)
METHYLPREDNISOLONE	18 (7.4%)	41 (8.5%)	59 (8.2%)
SALBUTAMOL	18 (7.4%)	35 (7.3%)	53 (7.3%)
IPRATROPIUM BROMIDE	16 (6.6%)	36 (7.5%)	52 (7.2%)
LEVOFLOXACIN	18 (7.4%)	31 (6.5%)	49 (6.8%)
CLARITHROMYCIN	17 (7.0%)	31 (6.5%)	48 (6.6%)
MOXIFLOXACIN	11 (4.5%)	37 (7.7%)	48 (6.6%)
AMOXICILLIN	13 (5.3%)	34 (7.1%)	47 (6.5%)
CEFUROXIME AXETIL	15 (6.2%)	32 (6.7%)	47 (6.5%)
FLUTICASONE PROPIONATE	9 (3.7%)	27 (5.6%)	36 (5.0%)
BUDESONIDE	14 (5.8%)	21 (4.4%)	35 (4.8%)
DEFLAZACORT	10 (4.1%)	25 (5.2%)	35 (4.8%)
CARBOCISTEINE	14 (5.8%)	20 (4.2%)	34 (4.7%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT COPD MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. COPD EXACERBATION MEDICATION IS DEFINED AS MEDICATION INITIATED ON OR AFTER VISIT 1 OF STUDY 040 AND WHERE THE INDICATION = COPD EXACERBATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10C

SUMMARY OF CONCOMITANT MEDICATIONS GIVEN FOR EXACERBATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
CEFIXIME	11 (4.5%)	21 (4.4%)	32 (4.4%)
PREDNISOLONE SODIUM SULFOBENZOATE	10 (4.1%)	21 (4.4%)	31 (4.3%)
ROXITHROMYCIN	10 (4.1%)	20 (4.2%)	30 (4.1%)
FORMOTEROL FUMARATE	9 (3.7%)	20 (4.2%)	29 (4.0%)
CIPROFLOXACIN	4 (1.6%)	22 (4.6%)	26 (3.6%)
CEFTRIAXONE SODIUM	9 (3.7%)	13 (2.7%)	22 (3.0%)
AMBROXOL HYDROCHLORIDE	9 (3.7%)	12 (2.5%)	21 (2.9%)
CIPROFLOXACIN HYDROCHLORIDE	10 (4.1%)	10 (2.1%)	20 (2.8%)
THEOPHYLLINE	4 (1.6%)	15 (3.1%)	19 (2.6%)
ERYTHROMYCIN	3 (1.2%)	15 (3.1%)	18 (2.5%)
OMEPRAZOLE	3 (1.2%)	15 (3.1%)	18 (2.5%)
METHYLPREDNISOLONE SODIUM SUCCINATE	4 (1.6%)	12 (2.5%)	16 (2.2%)
BETAMETHASONE SODIUM PHOSPHATE	2 (0.8%)	12 (2.5%)	14 (1.9%)
CEFPODOXIME PROXETIL	5 (2.1%)	9 (1.9%)	14 (1.9%)
DOXYCYCLINE	2 (0.8%)	12 (2.5%)	14 (1.9%)
SALMETEROL	5 (2.1%)	9 (1.9%)	14 (1.9%)
SALMETEROL XINAFOATE	3 (1.2%)	11 (2.3%)	14 (1.9%)
ACETYLSALICYLIC ACID	4 (1.6%)	9 (1.9%)	13 (1.8%)
AMBROXOL	3 (1.2%)	10 (2.1%)	13 (1.8%)
CODEINE PHOSPHATE	3 (1.2%)	10 (2.1%)	13 (1.8%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT COPD MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. COPD EXACERBATION MEDICATION IS DEFINED AS MEDICATION INITIATED ON OR AFTER VISIT 1 OF STUDY 040 AND WHERE THE INDICATION = COPD EXACERBATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

SB 207499

TABLE 13.10C

SUMMARY OF CONCOMITANT MEDICATIONS GIVEN FOR EXACERBATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
FLUTICASONE	3 (1.2%)	9 (1.9%)	12 (1.7%)
PREDNISOLONE SODIUM SUCCINATE	2 (0.8%)	10 (2.1%)	12 (1.7%)
TRIMETHOPRIM	3 (1.2%)	9 (1.9%)	12 (1.7%)
CLOPERASTINE HYDROCHLORIDE	4 (1.6%)	7 (1.5%)	11 (1.5%)
FORMOTEROL	3 (1.2%)	8 (1.7%)	11 (1.5%)
OFLOXACIN	2 (0.8%)	9 (1.9%)	11 (1.5%)
PHENYLEPHRINE HYDROCHLORIDE	6 (2.5%)	5 (1.0%)	11 (1.5%)
PRISTINAMYCIN	1 (0.4%)	10 (2.1%)	11 (1.5%)
RANITIDINE HYDROCHLORIDE	3 (1.2%)	8 (1.7%)	11 (1.5%)
BETAMETHASONE ACETATE	1 (0.4%)	9 (1.9%)	10 (1.4%)
CEFACTOR	4 (1.6%)	6 (1.3%)	10 (1.4%)
CIPROFLOXACIN LACTATE	2 (0.8%)	8 (1.7%)	10 (1.4%)
OXYGEN	4 (1.6%)	6 (1.3%)	10 (1.4%)
PHOLCODINE	3 (1.2%)	7 (1.5%)	10 (1.4%)
SALBUTAMOL SULFATE	5 (2.1%)	5 (1.0%)	10 (1.4%)
SALMETEROL HYDROXYNAPHTHOATE	3 (1.2%)	7 (1.5%)	10 (1.4%)
TERBUTALINE SULFATE	4 (1.6%)	6 (1.3%)	10 (1.4%)
CEFUROXIME	3 (1.2%)	6 (1.3%)	9 (1.2%)
CLAVULANATE POTASSIUM	5 (2.1%)	4 (0.8%)	9 (1.2%)
GUAIFENESIN	5 (2.1%)	4 (0.8%)	9 (1.2%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT COPD MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. COPD EXACERBATION MEDICATION IS DEFINED AS MEDICATION INITIATED ON OR AFTER VISIT 1 OF STUDY 040 AND WHERE THE INDICATION = COPD EXACERBATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10C

SUMMARY OF CONCOMITANT MEDICATIONS GIVEN FOR EXACERBATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
CINEOLE	3 (1.2%)	5 (1.0%)	8 (1.1%)
DOXYCYCLINE HYDROCHLORIDE	5 (2.1%)	3 (0.6%)	8 (1.1%)
IBUPROFEN	4 (1.6%)	4 (0.8%)	8 (1.1%)
PSEUDOEPHEDRINE HYDROCHLORIDE	1 (0.4%)	7 (1.5%)	8 (1.1%)
SODIUM CITRATE	3 (1.2%)	5 (1.0%)	8 (1.1%)
AMMONIUM CHLORIDE	3 (1.2%)	4 (0.8%)	7 (1.0%)
ASCORBIC ACID	2 (0.8%)	5 (1.0%)	7 (1.0%)
BROMPHENIRAMINE MALEATE	6 (2.5%)	1 (0.2%)	7 (1.0%)
CEFOTIAM HEXETIL HYDROCHLORIDE	5 (2.1%)	2 (0.4%)	7 (1.0%)
CODEINE	4 (1.6%)	3 (0.6%)	7 (1.0%)
ENOXAPARIN	1 (0.4%)	6 (1.3%)	7 (1.0%)
IPRATROPIUM HYDROXIDE	3 (1.2%)	4 (0.8%)	7 (1.0%)
PHENYLPROPANOLAMINE HYDROCHLORIDE	5 (2.1%)	2 (0.4%)	7 (1.0%)
TIAPROFENIC ACID	3 (1.2%)	4 (0.8%)	7 (1.0%)
BELLADONNA EXTRACT	2 (0.8%)	4 (0.8%)	6 (0.8%)
BETAMETHASONE	4 (1.6%)	2 (0.4%)	6 (0.8%)
BROMHEXINE HYDROCHLORIDE	4 (1.6%)	2 (0.4%)	6 (0.8%)
DEXTROMETHORPHAN HYDROBROMIDE	2 (0.8%)	4 (0.8%)	6 (0.8%)
FENOTEROL HYDROBROMIDE	2 (0.8%)	4 (0.8%)	6 (0.8%)
GUAIACOL	2 (0.8%)	4 (0.8%)	6 (0.8%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT COPD MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. COPD EXACERBATION MEDICATION IS DEFINED AS MEDICATION INITIATED ON OR AFTER VISIT 1 OF STUDY 040 AND WHERE THE INDICATION = COPD EXACERBATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10C

SUMMARY OF CONCOMITANT MEDICATIONS GIVEN FOR EXACERBATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
SODIUM CAMSYLATE	2 (0.8%)	4 (0.8%)	6 (0.8%)
BISACODYL	3 (1.2%)	2 (0.4%)	5 (0.7%)
CEFAZOLIN SODIUM	2 (0.8%)	3 (0.6%)	5 (0.7%)
CEFTRIAXONE	2 (0.8%)	3 (0.6%)	5 (0.7%)
CHLORPHENAMINE MALEATE	2 (0.8%)	3 (0.6%)	5 (0.7%)
FUROSEMIDE	1 (0.4%)	4 (0.8%)	5 (0.7%)
LANSOPRAZOLE	2 (0.8%)	3 (0.6%)	5 (0.7%)
MENTHOL	3 (1.2%)	2 (0.4%)	5 (0.7%)
REPROTEROL HYDROCHLORIDE	1 (0.4%)	4 (0.8%)	5 (0.7%)
TRIPROLIDINE HYDROCHLORIDE	1 (0.4%)	4 (0.8%)	5 (0.7%)
BECLOMETASONE DIPROPIONATE	2 (0.8%)	2 (0.4%)	4 (0.6%)
BENZOIC ACID	3 (1.2%)	1 (0.2%)	4 (0.6%)
CALCIUM PANTOTHENATE	1 (0.4%)	3 (0.6%)	4 (0.6%)
CEFALEXIN	1 (0.4%)	3 (0.6%)	4 (0.6%)
CEFIXIME TRIHYDRATE	1 (0.4%)	3 (0.6%)	4 (0.6%)
DIPHENHYDRAMINE HYDROCHLORIDE	1 (0.4%)	3 (0.6%)	4 (0.6%)
DOXYCYCLINE HYCLATE	2 (0.8%)	2 (0.4%)	4 (0.6%)
EPHEDRINE HYDROCHLORIDE	3 (1.2%)	1 (0.2%)	4 (0.6%)
ERDOSTEINE	3 (1.2%)	1 (0.2%)	4 (0.6%)
FENSPIRIDE HYDROCHLORIDE	2 (0.8%)	2 (0.4%)	4 (0.6%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT COPD MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. COPD EXACERBATION MEDICATION IS DEFINED AS MEDICATION INITIATED ON OR AFTER VISIT 1 OF STUDY 040 AND WHERE THE INDICATION = COPD EXACERBATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10C

SUMMARY OF CONCOMITANT MEDICATIONS GIVEN FOR EXACERBATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
GENTAMICIN SULFATE	3 (1.2%)	1 (0.2%)	4 (0.6%)
NYSTATIN	2 (0.8%)	2 (0.4%)	4 (0.6%)
PYRIDOXINE HYDROCHLORIDE	2 (0.8%)	2 (0.4%)	4 (0.6%)
RANITIDINE	0 .	4 (0.8%)	4 (0.6%)
RIBOFLAVIN	2 (0.8%)	2 (0.4%)	4 (0.6%)
SULFAMETHOXAZOLE	1 (0.4%)	3 (0.6%)	4 (0.6%)
AMINOPHYLLINE	1 (0.4%)	2 (0.4%)	3 (0.4%)
CAFFEINE	1 (0.4%)	2 (0.4%)	3 (0.4%)
CARQUEJA	2 (0.8%)	1 (0.2%)	3 (0.4%)
CEFETAMET	0 .	3 (0.6%)	3 (0.4%)
CEFONICIDE SODIUM	1 (0.4%)	2 (0.4%)	3 (0.4%)
CROMOGLICATE SODIUM	1 (0.4%)	2 (0.4%)	3 (0.4%)
DEXAMETHASONE	0 .	3 (0.6%)	3 (0.4%)
DIMETOTIAZINE	2 (0.8%)	1 (0.2%)	3 (0.4%)
DIPHENYLPYRALINE HYDROCHLORIDE	2 (0.8%)	1 (0.2%)	3 (0.4%)
EUCALYPTUS OIL	2 (0.8%)	1 (0.2%)	3 (0.4%)
FLUCONAZOLE	3 (1.2%)	0 .	3 (0.4%)
HEXOPRENALINE SULFATE	2 (0.8%)	1 (0.2%)	3 (0.4%)
IPECACUANHA	2 (0.8%)	1 (0.2%)	3 (0.4%)
MEPYRAMINE THEOPHYLLINE ACETATE	0 .	3 (0.6%)	3 (0.4%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT COPD MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. COPD EXACERBATION MEDICATION IS DEFINED AS MEDICATION INITIATED ON OR AFTER VISIT 1 OF STUDY 040 AND WHERE THE INDICATION = COPD EXACERBATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10C

SUMMARY OF CONCOMITANT MEDICATIONS GIVEN FOR EXACERBATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
METAMIZOLE	2 (0.8%)	1 (0.2%)	3 (0.4%)
METAMIZOLE SODIUM	0 .	3 (0.6%)	3 (0.4%)
MIKANIA GLOMERATA	2 (0.8%)	1 (0.2%)	3 (0.4%)
NAPROXEN SODIUM	2 (0.8%)	1 (0.2%)	3 (0.4%)
NICOTINAMIDE	2 (0.8%)	1 (0.2%)	3 (0.4%)
SODIUM BENZOATE	0 .	3 (0.6%)	3 (0.4%)
TELITHROMYCIN	0 .	3 (0.6%)	3 (0.4%)
TERBUTALINE	0 .	3 (0.6%)	3 (0.4%)
THIAMINE HYDROCHLORIDE	1 (0.4%)	2 (0.4%)	3 (0.4%)
THIAMPHENICOL	3 (1.2%)	0 .	3 (0.4%)
VITAMINS NOS	2 (0.8%)	1 (0.2%)	3 (0.4%)
ALUMINIUM	0 .	2 (0.4%)	2 (0.3%)
AMPHOTERICIN B	1 (0.4%)	1 (0.2%)	2 (0.3%)
ANTIBIOTIC NOS	1 (0.4%)	1 (0.2%)	2 (0.3%)
BACITRACIN	0 .	2 (0.4%)	2 (0.3%)
BECLOMETASONE	1 (0.4%)	1 (0.2%)	2 (0.3%)
BISMUTH	0 .	2 (0.4%)	2 (0.3%)
CAFFEINE CITRATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
CEFALEXIN MONOHYDRATE	2 (0.8%)	0 .	2 (0.3%)
CEFATRIZINE	1 (0.4%)	1 (0.2%)	2 (0.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT COPD MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
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TABLE 13.10C

SUMMARY OF CONCOMITANT MEDICATIONS GIVEN FOR EXACERBATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
CEFTIBUTEN	0 .	2 (0.4%)	2 (0.3%)
CEFUROXIME SODIUM	2 (0.8%)	0 .	2 (0.3%)
CETRIMONIUM BROMIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
COCILLANA LIQUID EXTRACT	2 (0.8%)	0 .	2 (0.3%)
CODEINE HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
ETHYLENEDIAMINE	1 (0.4%)	1 (0.2%)	2 (0.3%)
ETHYLMORPHINE HYDROCHLORIDE	2 (0.8%)	0 .	2 (0.3%)
GENTIAN	0 .	2 (0.4%)	2 (0.3%)
HEPARIN-FRACTION, CALCIUM SALT	0 .	2 (0.4%)	2 (0.3%)
HEPARIN-FRACTION, SODIUM SALT	1 (0.4%)	1 (0.2%)	2 (0.3%)
HYDROCODONE BITARTRATE	0 .	2 (0.4%)	2 (0.3%)
IMMUNOGLOBULIN HUMAN NORMAL	2 (0.8%)	0 .	2 (0.3%)
KETOCONAZOLE	1 (0.4%)	1 (0.2%)	2 (0.3%)
LYMECYCLINE	1 (0.4%)	1 (0.2%)	2 (0.3%)
LYSOZYME	0 .	2 (0.4%)	2 (0.3%)
MAGNESIUM NOS	0 .	2 (0.4%)	2 (0.3%)
MESNA	2 (0.8%)	0 .	2 (0.3%)
MINERALS NOS	2 (0.8%)	0 .	2 (0.3%)
NAPHAZOLINE NITRATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
OXYTETRACYCLINE	1 (0.4%)	1 (0.2%)	2 (0.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT COPD MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
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TABLE 13.10C

SUMMARY OF CONCOMITANT MEDICATIONS GIVEN FOR EXACERBATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
PAPAIN	0 .	2 (0.4%)	2 (0.3%)
PAPAVERINE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)
PENICILLIN NOS	1 (0.4%)	1 (0.2%)	2 (0.3%)
PENTOXYVERINE CITRATE	0 .	2 (0.4%)	2 (0.3%)
PHENOXYMETHYLPENICILLIN POTASSIUM	1 (0.4%)	1 (0.2%)	2 (0.3%)
PRIMULA FLOWERS	0 .	2 (0.4%)	2 (0.3%)
RUMICIS ASETOSA	0 .	2 (0.4%)	2 (0.3%)
SALICYLAMIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
SAMBUCUS FLOWERS	0 .	2 (0.4%)	2 (0.3%)
SPIRONOLACTONE	0 .	2 (0.4%)	2 (0.3%)
VERBENA HERB	0 .	2 (0.4%)	2 (0.3%)
ACONITE TINCTURE	0 .	1 (0.2%)	1 (0.1%)
AMANTADINE HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)
AMILORIDE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
AMINOBENZOIC ACID	0 .	1 (0.2%)	1 (0.1%)
AMOBARBITAL	0 .	1 (0.2%)	1 (0.1%)
AMPICILLIN	0 .	1 (0.2%)	1 (0.1%)
ANISATED SPIRIT OF AMMONIA	0 .	1 (0.2%)	1 (0.1%)
ATROPINE BORATE	1 (0.4%)	0 .	1 (0.1%)
BAMBUTEROL HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT COPD MEDICATION
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TABLE 13.10C

SUMMARY OF CONCOMITANT MEDICATIONS GIVEN FOR EXACERBATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
BELLADONNA TINCTURE	0 .	1 (0.2%)	1 (0.1%)
BENZALKONIUM CHLORIDE	0 .	1 (0.2%)	1 (0.1%)
BISMUTH CAMPHOCARBONATE	0 .	1 (0.2%)	1 (0.1%)
BROMHEXINE	1 (0.4%)	0 .	1 (0.1%)
BUMETANIDE	0 .	1 (0.2%)	1 (0.1%)
BUTACAINE SULPHATE	1 (0.4%)	0 .	1 (0.1%)
BUTETAMATE CITRATE	0 .	1 (0.2%)	1 (0.1%)
BUZEPIDE METHYLHYDROXIDE	0 .	1 (0.2%)	1 (0.1%)
CAJEPUTOL OIL	1 (0.4%)	0 .	1 (0.1%)
CAMPHOR	1 (0.4%)	0 .	1 (0.1%)
CAPTOPRIL	0 .	1 (0.2%)	1 (0.1%)
CEDAR OIL	1 (0.4%)	0 .	1 (0.1%)
CEFADROXIL	1 (0.4%)	0 .	1 (0.1%)
CEFAPIRIN SODIUM	1 (0.4%)	0 .	1 (0.1%)
CEFEPIM	0 .	1 (0.2%)	1 (0.1%)
CEFOTIAM	0 .	1 (0.2%)	1 (0.1%)
CEFPROZIL MONOHYDRATE	0 .	1 (0.2%)	1 (0.1%)
CEFRADINE	0 .	1 (0.2%)	1 (0.1%)
CELECOXIB	0 .	1 (0.2%)	1 (0.1%)
CHLORCYCLIZINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT COPD MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. COPD EXACERBATION MEDICATION IS DEFINED AS MEDICATION INITIATED ON OR AFTER VISIT 1 OF STUDY 040 AND WHERE THE INDICATION = COPD EXACERBATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10C

SUMMARY OF CONCOMITANT MEDICATIONS GIVEN FOR EXACERBATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
CHLOROPHYLL	1 (0.4%)	0 .	1 (0.1%)
CHOLINE BITARTRATE	0 .	1 (0.2%)	1 (0.1%)
CHOLINE THEOPHYLLINATE	0 .	1 (0.2%)	1 (0.1%)
CIMICIFUGA	0 .	1 (0.2%)	1 (0.1%)
CLAVULANATE	0 .	1 (0.2%)	1 (0.1%)
CYANOCOBALAMIN	0 .	1 (0.2%)	1 (0.1%)
DESONIDE	1 (0.4%)	0 .	1 (0.1%)
DEXCHLORPHENIRAMINE MALEATE	0 .	1 (0.2%)	1 (0.1%)
DEXTROPROPOXYPHENE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
DEXTROSE PARENTERALS	0 .	1 (0.2%)	1 (0.1%)
DIETHYLAMINE SALICYLATE	1 (0.4%)	0 .	1 (0.1%)
DIGOXIN	1 (0.4%)	0 .	1 (0.1%)
DILTIAZEM	1 (0.4%)	0 .	1 (0.1%)
DIMEMORFAN PHOSPHATE	1 (0.4%)	0 .	1 (0.1%)
DIPROPHYLLINE	0 .	1 (0.2%)	1 (0.1%)
DOMPERIDONE	0 .	1 (0.2%)	1 (0.1%)
DOXAZOSIN	0 .	1 (0.2%)	1 (0.1%)
ENALAPRIL MALEATE	0 .	1 (0.2%)	1 (0.1%)
EPINEPHRINE	0 .	1 (0.2%)	1 (0.1%)
EPRAZINONE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT COPD MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. COPD EXACERBATION MEDICATION IS DEFINED AS MEDICATION INITIATED ON OR AFTER VISIT 1 OF STUDY 040 AND WHERE THE INDICATION = COPD EXACERBATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

SB 207499

TABLE 13.10C

SUMMARY OF CONCOMITANT MEDICATIONS GIVEN FOR EXACERBATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
ERYTHROMYCIN ETHYLSUCCINATE	0 .	1 (0.2%)	1 (0.1%)
ERYTHROMYCIN STEARATE	0 .	1 (0.2%)	1 (0.1%)
ESCIN	1 (0.4%)	0 .	1 (0.1%)
ETHYLMORPHINE	0 .	1 (0.2%)	1 (0.1%)
EUPHORBIA	1 (0.4%)	0 .	1 (0.1%)
EUPHORBIA LIQUID EXTRACT	1 (0.4%)	0 .	1 (0.1%)
EXPECTORANTS NOS	0 .	1 (0.2%)	1 (0.1%)
FAMOTIDINE	0 .	1 (0.2%)	1 (0.1%)
FLUCLOXACILLIN	1 (0.4%)	0 .	1 (0.1%)
FLUOCINOLONE ACETONIDE	0 .	1 (0.2%)	1 (0.1%)
FLUOCORTOLONE	1 (0.4%)	0 .	1 (0.1%)
FLUOCORTOLONE CAPROATE	1 (0.4%)	0 .	1 (0.1%)
FOLIC ACID	0 .	1 (0.2%)	1 (0.1%)
FRANGULA EXTRACT	1 (0.4%)	0 .	1 (0.1%)
FRANGULIN	1 (0.4%)	0 .	1 (0.1%)
FUSAFUNGINE	1 (0.4%)	0 .	1 (0.1%)
GLIMEPIRIDE	1 (0.4%)	0 .	1 (0.1%)
GLUCOSE	1 (0.4%)	0 .	1 (0.1%)
GLYCEROL	0 .	1 (0.2%)	1 (0.1%)
GREPAFLOXACIN HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT COPD MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. COPD EXACERBATION MEDICATION IS DEFINED AS MEDICATION INITIATED ON OR AFTER VISIT 1 OF STUDY 040 AND WHERE THE INDICATION = COPD EXACERBATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10C

SUMMARY OF CONCOMITANT MEDICATIONS GIVEN FOR EXACERBATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
GRINDELIA	0 .	1 (0.2%)	1 (0.1%)
HELICIDINE	0 .	1 (0.2%)	1 (0.1%)
HEXAMIDINE ISETHIONATE	1 (0.4%)	0 .	1 (0.1%)
HYDROCHLOROTHIAZIDE	0 .	1 (0.2%)	1 (0.1%)
HYDROCORTISONE	0 .	1 (0.2%)	1 (0.1%)
HYDROCORTISONE SODIUM PHOSPHATE	0 .	1 (0.2%)	1 (0.1%)
HYDROCORTISONE SODIUM SUCCINATE	0 .	1 (0.2%)	1 (0.1%)
HYDROXYETHYL THEOPHYLLINE	0 .	1 (0.2%)	1 (0.1%)
HYDROXYZINE HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)
HYOSCYAMINE SULFATE	0 .	1 (0.2%)	1 (0.1%)
INOSITOL	0 .	1 (0.2%)	1 (0.1%)
IPRATROPIUM	0 .	1 (0.2%)	1 (0.1%)
ISOSORBIDE DINITRATE	1 (0.4%)	0 .	1 (0.1%)
JOSAMYCIN	0 .	1 (0.2%)	1 (0.1%)
KETOPROFEN	1 (0.4%)	0 .	1 (0.1%)
LACTOBACILLUS LACTIS	1 (0.4%)	0 .	1 (0.1%)
LACTUCA EXTRACT	1 (0.4%)	0 .	1 (0.1%)
LACTUCA SYRUP	1 (0.4%)	0 .	1 (0.1%)
LECITHIN	0 .	1 (0.2%)	1 (0.1%)
LIDOCAINE HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT COPD MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. COPD EXACERBATION MEDICATION IS DEFINED AS MEDICATION INITIATED ON OR AFTER VISIT 1 OF STUDY 040 AND WHERE THE INDICATION = COPD EXACERBATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10C

SUMMARY OF CONCOMITANT MEDICATIONS GIVEN FOR EXACERBATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
LORACARBEF	0 .	1 (0.2%)	1 (0.1%)
LORATADINE	1 (0.4%)	0 .	1 (0.1%)
LORMETAZEPAM	1 (0.4%)	0 .	1 (0.1%)
METRONIDAZOLE	1 (0.4%)	0 .	1 (0.1%)
MIDAZOLAM MALEATE	1 (0.4%)	0 .	1 (0.1%)
MIDECAMYCIN	0 .	1 (0.2%)	1 (0.1%)
MIOKAMYCIN	0 .	1 (0.2%)	1 (0.1%)
MOMETASONE FUROATE	1 (0.4%)	0 .	1 (0.1%)
MONTELUKAST SODIUM	0 .	1 (0.2%)	1 (0.1%)
MOROXYDINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
MORPHINE SULFATE	0 .	1 (0.2%)	1 (0.1%)
MULTIMINERALS	1 (0.4%)	0 .	1 (0.1%)
MULTIVITAMINS, NOS	1 (0.4%)	0 .	1 (0.1%)
MYRTOL	0 .	1 (0.2%)	1 (0.1%)
NEBIVOLOL HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
NEOMYCIN SULFATE	0 .	1 (0.2%)	1 (0.1%)
NIMESULIDE	1 (0.4%)	0 .	1 (0.1%)
NUTMEG OIL	1 (0.4%)	0 .	1 (0.1%)
OXITROPIUM BROMIDE	1 (0.4%)	0 .	1 (0.1%)
OXOMEMAZINE	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT COPD MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. COPD EXACERBATION MEDICATION IS DEFINED AS MEDICATION INITIATED ON OR AFTER VISIT 1 OF STUDY 040 AND WHERE THE INDICATION = COPD EXACERBATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10C

SUMMARY OF CONCOMITANT MEDICATIONS GIVEN FOR EXACERBATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
PENTETRAZOL	0 .	1 (0.2%)	1 (0.1%)
PENTOSAN POLYSULFATE	1 (0.4%)	0 .	1 (0.1%)
PHENAZONE	0 .	1 (0.2%)	1 (0.1%)
PHENIRAMINE MALEATE	0 .	1 (0.2%)	1 (0.1%)
PIMPINELLA ROOT	0 .	1 (0.2%)	1 (0.1%)
PINE OIL	0 .	1 (0.2%)	1 (0.1%)
PNEUMOCOCCAL VACCINE	0 .	1 (0.2%)	1 (0.1%)
POLYGALA AMARA TINCTURE	0 .	1 (0.2%)	1 (0.1%)
POLYGALA SENEGA	1 (0.4%)	0 .	1 (0.1%)
PREDNISOLONE ACETATE	0 .	1 (0.2%)	1 (0.1%)
PRIMULA RHIZOME	0 .	1 (0.2%)	1 (0.1%)
PROCAINE	0 .	1 (0.2%)	1 (0.1%)
PROCHLORPERAZINE	1 (0.4%)	0 .	1 (0.1%)
PROPACETAMOL HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
QUEBRACHO BARK	0 .	1 (0.2%)	1 (0.1%)
RITIOMETAN	0 .	1 (0.2%)	1 (0.1%)
ROFECOXIB	0 .	1 (0.2%)	1 (0.1%)
ROSEMARY OIL	0 .	1 (0.2%)	1 (0.1%)
ROXATIDINE HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)
SACCHAROMYCES BOULARDII	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT COPD MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. COPD EXACERBATION MEDICATION IS DEFINED AS MEDICATION INITIATED ON OR AFTER VISIT 1 OF STUDY 040 AND WHERE THE INDICATION = COPD EXACERBATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

SB 207499

TABLE 13.10C

SUMMARY OF CONCOMITANT MEDICATIONS GIVEN FOR EXACERBATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
SILVER NITRATE	0 .	1 (0.2%)	1 (0.1%)
SODIUM BROMIDE	0 .	1 (0.2%)	1 (0.1%)
SODIUM CHLORIDE	1 (0.4%)	0 .	1 (0.1%)
SODIUM LACTATE COMPOUND INJECTION	1 (0.4%)	0 .	1 (0.1%)
SQUILL EXTRACT	1 (0.4%)	0 .	1 (0.1%)
SQUILL SYRUP COMPOUND	1 (0.4%)	0 .	1 (0.1%)
SUCRALFATE	1 (0.4%)	0 .	1 (0.1%)
SULFADIAZINE	0 .	1 (0.2%)	1 (0.1%)
SULPHANILAMIDE	1 (0.4%)	0 .	1 (0.1%)
TERPIN HYDRATE	0 .	1 (0.2%)	1 (0.1%)
TERPINEOL	0 .	1 (0.2%)	1 (0.1%)
THIAMINE MONONITRATE	1 (0.4%)	0 .	1 (0.1%)
THYME EXTRACT	0 .	1 (0.2%)	1 (0.1%)
THYME OIL	0 .	1 (0.2%)	1 (0.1%)
TIXOCORTOL PIVALATE	0 .	1 (0.2%)	1 (0.1%)
TRAMADOL HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
TRIAMCINOLONE	0 .	1 (0.2%)	1 (0.1%)
TRIAMCINOLONE ACETONIDE	0 .	1 (0.2%)	1 (0.1%)
TUAMINOHEPTANE SULFATE	0 .	1 (0.2%)	1 (0.1%)
UNKNOWN MEDICATION	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT COPD MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. COPD EXACERBATION MEDICATION IS DEFINED AS MEDICATION INITIATED ON OR AFTER VISIT 1 OF STUDY 040 AND WHERE THE INDICATION = COPD EXACERBATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10C

SUMMARY OF CONCOMITANT MEDICATIONS GIVEN FOR EXACERBATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
URIDINE TRIPHOSPHATE SODIUM	0 .	1 (0.2%)	1 (0.1%)
VERAPAMIL HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)
YEAST DRIED	0 .	1 (0.2%)	1 (0.1%)
ZANAMIVIR	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT COPD MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. COPD EXACERBATION MEDICATION IS DEFINED AS MEDICATION INITIATED ON OR AFTER VISIT 1 OF STUDY 040 AND WHERE THE INDICATION = COPD EXACERBATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
TOTAL	243 (100.0%)	479 (99.8%)	722 (99.9%)
SALBUTAMOL	228 (93.8%)	442 (92.1%)	670 (92.7%)
IPRATROPIUM BROMIDE	117 (48.1%)	228 (47.5%)	345 (47.7%)
PARACETAMOL	81 (33.3%)	175 (36.5%)	256 (35.4%)
AMOXICILLIN	82 (33.7%)	168 (35.0%)	250 (34.6%)
CLAVULANIC ACID	49 (20.2%)	110 (22.9%)	159 (22.0%)
ACETYLCYSTEINE	47 (19.3%)	91 (19.0%)	138 (19.1%)
ACETYLSALICYLIC ACID	40 (16.5%)	83 (17.3%)	123 (17.0%)
INFLUENZA VIRUS VACCINE POLYVALENT	47 (19.3%)	76 (15.8%)	123 (17.0%)
SALMETEROL	42 (17.3%)	80 (16.7%)	122 (16.9%)
FORMOTEROL	40 (16.5%)	74 (15.4%)	114 (15.8%)
METHYLPREDNISOLONE	31 (12.8%)	69 (14.4%)	100 (13.8%)
PREDNISOLONE	34 (14.0%)	65 (13.5%)	99 (13.7%)
OMEPRAZOLE	29 (11.9%)	67 (14.0%)	96 (13.3%)
AZITHROMYCIN	37 (15.2%)	54 (11.3%)	91 (12.6%)
BUDESONIDE	36 (14.8%)	52 (10.8%)	88 (12.2%)
CIPROFLOXACIN	30 (12.3%)	54 (11.3%)	84 (11.6%)
PREDNISONE	28 (11.5%)	55 (11.5%)	83 (11.5%)
FLUTICASONE PROPIONATE	27 (11.1%)	55 (11.5%)	82 (11.3%)
CEFUROXIME	24 (9.9%)	52 (10.8%)	76 (10.5%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
RANITIDINE	27 (11.1%)	48 (10.0%)	75 (10.4%)
CLARITHROMYCIN	21 (8.6%)	51 (10.6%)	72 (10.0%)
DICLOFENAC	24 (9.9%)	44 (9.2%)	68 (9.4%)
CODEINE PHOSPHATE	15 (6.2%)	49 (10.2%)	64 (8.9%)
LEVOFLOXACIN	22 (9.1%)	39 (8.1%)	61 (8.4%)
IBUPROFEN	20 (8.2%)	39 (8.1%)	59 (8.2%)
MOXIFLOXACIN	13 (5.3%)	44 (9.2%)	57 (7.9%)
BETAMETHASONE	15 (6.2%)	35 (7.3%)	50 (6.9%)
CARBOCISTEINE	18 (7.4%)	31 (6.5%)	49 (6.8%)
FUROSEMIDE	18 (7.4%)	31 (6.5%)	49 (6.8%)
METAMIZOLE	11 (4.5%)	34 (7.1%)	45 (6.2%)
HYDROCHLOROTHIAZIDE	15 (6.2%)	29 (6.0%)	44 (6.1%)
ENALAPRIL	12 (4.9%)	31 (6.5%)	43 (5.9%)
ROXITHROMYCIN	13 (5.3%)	29 (6.0%)	42 (5.8%)
ASCORBIC ACID	13 (5.3%)	28 (5.8%)	41 (5.7%)
CEFIXIME	15 (6.2%)	26 (5.4%)	41 (5.7%)
DEFLAZACORT	14 (5.8%)	27 (5.6%)	41 (5.7%)
ALLOPURINOL	16 (6.6%)	23 (4.8%)	39 (5.4%)
GLYCERYL TRINITRATE	14 (5.8%)	24 (5.0%)	38 (5.3%)
DEXTROPROPOXYPHENE HYDROCHLORIDE	14 (5.8%)	22 (4.6%)	36 (5.0%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
THEOPHYLLINE	7 (2.9%)	29 (6.0%)	36 (5.0%)
ALMAGATE	14 (5.8%)	21 (4.4%)	35 (4.8%)
AMBROXOL HYDROCHLORIDE	15 (6.2%)	20 (4.2%)	35 (4.8%)
CAFFEINE	8 (3.3%)	27 (5.6%)	35 (4.8%)
PREDNISOLONE SODIUM SULFOBENZOATE	12 (4.9%)	23 (4.8%)	35 (4.8%)
CALCIUM SACCHARATE	13 (5.3%)	21 (4.4%)	34 (4.7%)
CEFTRIAXONE	15 (6.2%)	19 (4.0%)	34 (4.7%)
FLUTICASONE	11 (4.5%)	21 (4.4%)	32 (4.4%)
TRIMETHOPRIM	6 (2.5%)	24 (5.0%)	30 (4.1%)
SODIUM BICARBONATE	9 (3.7%)	20 (4.2%)	29 (4.0%)
BECLOMETASONE	12 (4.9%)	16 (3.3%)	28 (3.9%)
ERYTHROMYCIN	3 (1.2%)	25 (5.2%)	28 (3.9%)
SIMVASTATIN	11 (4.5%)	17 (3.5%)	28 (3.9%)
NIFEDIPINE	6 (2.5%)	21 (4.4%)	27 (3.7%)
VERAPAMIL	9 (3.7%)	18 (3.8%)	27 (3.7%)
CAPTOPRIL	9 (3.7%)	17 (3.5%)	26 (3.6%)
LORATADINE	9 (3.7%)	16 (3.3%)	25 (3.5%)
DIGOXIN	10 (4.1%)	14 (2.9%)	24 (3.3%)
DILTIAZEM HYDROCHLORIDE	6 (2.5%)	18 (3.8%)	24 (3.3%)
SODIUM CHLORIDE	12 (4.9%)	12 (2.5%)	24 (3.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
LANSOPRAZOLE	7 (2.9%)	16 (3.3%)	23 (3.2%)
POTASSIUM CHLORIDE	8 (3.3%)	15 (3.1%)	23 (3.2%)
ALUMINIUM HYDROXIDE	8 (3.3%)	14 (2.9%)	22 (3.0%)
CEFPODOXIME PROXETIL	7 (2.9%)	15 (3.1%)	22 (3.0%)
DIAZEPAM	8 (3.3%)	14 (2.9%)	22 (3.0%)
DOXYCYCLINE	5 (2.1%)	17 (3.5%)	22 (3.0%)
ENOXAPARIN	6 (2.5%)	16 (3.3%)	22 (3.0%)
FENOTEROL	4 (1.6%)	17 (3.5%)	21 (2.9%)
LORAZEPAM	8 (3.3%)	13 (2.7%)	21 (2.9%)
OXYGEN	9 (3.7%)	12 (2.5%)	21 (2.9%)
PHENYLEPHRINE HYDROCHLORIDE	10 (4.1%)	11 (2.3%)	21 (2.9%)
TERBUTALINE	4 (1.6%)	17 (3.5%)	21 (2.9%)
DEXAMETHASONE	7 (2.9%)	13 (2.7%)	20 (2.8%)
HEPARIN-FRACTION, CALCIUM SALT	5 (2.1%)	15 (3.1%)	20 (2.8%)
PIROXICAM	5 (2.1%)	15 (3.1%)	20 (2.8%)
SALICYLAMIDE	6 (2.5%)	14 (2.9%)	20 (2.8%)
AMBROXOL	6 (2.5%)	13 (2.7%)	19 (2.6%)
GLIBENCLAMIDE	5 (2.1%)	14 (2.9%)	19 (2.6%)
TRAMADOL HYDROCHLORIDE	5 (2.1%)	14 (2.9%)	19 (2.6%)
TRIAMCINOLONE ACETONIDE	5 (2.1%)	14 (2.9%)	19 (2.6%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
AMIODARONE HYDROCHLORIDE	7 (2.9%)	11 (2.3%)	18 (2.5%)
OFLOXACIN	5 (2.1%)	13 (2.7%)	18 (2.5%)
PNEUMOCOCCAL VACCINE	6 (2.5%)	12 (2.5%)	18 (2.5%)
BROMAZEPAM	8 (3.3%)	9 (1.9%)	17 (2.4%)
CHLORPHENAMINE MALEATE	5 (2.1%)	12 (2.5%)	17 (2.4%)
NYSTATIN	7 (2.9%)	10 (2.1%)	17 (2.4%)
SORBITOL	8 (3.3%)	9 (1.9%)	17 (2.4%)
ISOSORBIDE MONONITRATE	5 (2.1%)	11 (2.3%)	16 (2.2%)
SPIRONOLACTONE	7 (2.9%)	9 (1.9%)	16 (2.2%)
CLAVULANATE POTASSIUM	8 (3.3%)	7 (1.5%)	15 (2.1%)
CLOPIDOGREL	2 (0.8%)	13 (2.7%)	15 (2.1%)
CODEINE	6 (2.5%)	9 (1.9%)	15 (2.1%)
LIDOCAINE HYDROCHLORIDE	6 (2.5%)	9 (1.9%)	15 (2.1%)
MAGNESIUM TRISILICATE	6 (2.5%)	9 (1.9%)	15 (2.1%)
PHOLCODINE	5 (2.1%)	10 (2.1%)	15 (2.1%)
THIAMINE HYDROCHLORIDE	7 (2.9%)	8 (1.7%)	15 (2.1%)
ZOPICLONE	3 (1.2%)	12 (2.5%)	15 (2.1%)
ACETYLSALICYLATE LYSINE	4 (1.6%)	10 (2.1%)	14 (1.9%)
ALGINIC ACID	5 (2.1%)	9 (1.9%)	14 (1.9%)
AMLODIPINE BESYLATE	5 (2.1%)	9 (1.9%)	14 (1.9%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
ISOSORBIDE DINITRATE	4 (1.6%)	10 (2.1%)	14 (1.9%)
LISINOPRIL	5 (2.1%)	9 (1.9%)	14 (1.9%)
MENTHOL	3 (1.2%)	11 (2.3%)	14 (1.9%)
METFORMIN HYDROCHLORIDE	6 (2.5%)	8 (1.7%)	14 (1.9%)
MISOPROSTOL	5 (2.1%)	9 (1.9%)	14 (1.9%)
NEOMYCIN SULFATE	5 (2.1%)	9 (1.9%)	14 (1.9%)
PRISTINAMYCIN	2 (0.8%)	12 (2.5%)	14 (1.9%)
PROCHLORPERAZINE	5 (2.1%)	9 (1.9%)	14 (1.9%)
PYRIDOXINE HYDROCHLORIDE	6 (2.5%)	8 (1.7%)	14 (1.9%)
CELECOXIB	2 (0.8%)	11 (2.3%)	13 (1.8%)
DOXYCYCLINE HYDROCHLORIDE	8 (3.3%)	5 (1.0%)	13 (1.8%)
FENOFIBRATE	5 (2.1%)	8 (1.7%)	13 (1.8%)
FLUOXETINE	2 (0.8%)	11 (2.3%)	13 (1.8%)
GLUCOSE	6 (2.5%)	7 (1.5%)	13 (1.8%)
HYDROXYZINE HYDROCHLORIDE	5 (2.1%)	8 (1.7%)	13 (1.8%)
LACTULOSE	4 (1.6%)	9 (1.9%)	13 (1.8%)
MOLSIDOMINE	4 (1.6%)	9 (1.9%)	13 (1.8%)
PSEUDOEPHEDRINE HYDROCHLORIDE	3 (1.2%)	10 (2.1%)	13 (1.8%)
SODIUM CITRATE	3 (1.2%)	10 (2.1%)	13 (1.8%)
TAMSULOSIN HYDROCHLORIDE	6 (2.5%)	7 (1.5%)	13 (1.8%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
VITAMINS NOS	6 (2.5%)	7 (1.5%)	13 (1.8%)
ZOLPIDEM HEMITARTRATE	5 (2.1%)	8 (1.7%)	13 (1.8%)
ALGIN	4 (1.6%)	8 (1.7%)	12 (1.7%)
ATORVASTATIN	4 (1.6%)	8 (1.7%)	12 (1.7%)
ATORVASTATIN CALCIUM	9 (3.7%)	3 (0.6%)	12 (1.7%)
CEFACLOR	6 (2.5%)	6 (1.3%)	12 (1.7%)
LOPERAMIDE HYDROCHLORIDE	5 (2.1%)	7 (1.5%)	12 (1.7%)
METOCLOPRAMIDE	3 (1.2%)	9 (1.9%)	12 (1.7%)
PREDNISOLONE SODIUM SUCCINATE	2 (0.8%)	10 (2.1%)	12 (1.7%)
QUININE SULFATE	4 (1.6%)	8 (1.7%)	12 (1.7%)
ROFECOXIB	7 (2.9%)	5 (1.0%)	12 (1.7%)
AMLODIPINE	5 (2.1%)	6 (1.3%)	11 (1.5%)
BROMHEXINE HYDROCHLORIDE	5 (2.1%)	6 (1.3%)	11 (1.5%)
CALCIUM CARBONATE	7 (2.9%)	4 (0.8%)	11 (1.5%)
CHLORAMPHENICOL	5 (2.1%)	6 (1.3%)	11 (1.5%)
CLOPERASTINE HYDROCHLORIDE	4 (1.6%)	7 (1.5%)	11 (1.5%)
DOXAZOSIN	6 (2.5%)	5 (1.0%)	11 (1.5%)
GENTAMICIN SULFATE	6 (2.5%)	5 (1.0%)	11 (1.5%)
GUAIFENESIN	5 (2.1%)	6 (1.3%)	11 (1.5%)
IRBESARTAN	4 (1.6%)	7 (1.5%)	11 (1.5%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
KETOPROFEN	6 (2.5%)	5 (1.0%)	11 (1.5%)
LEVOTHYROXINE SODIUM	3 (1.2%)	8 (1.7%)	11 (1.5%)
LOSARTAN POTASSIUM	2 (0.8%)	9 (1.9%)	11 (1.5%)
NIMESULIDE	3 (1.2%)	8 (1.7%)	11 (1.5%)
SULFAMETHOXAZOLE	2 (0.8%)	9 (1.9%)	11 (1.5%)
TRIAMTERENE	6 (2.5%)	5 (1.0%)	11 (1.5%)
ACECLOFENAC	5 (2.1%)	5 (1.0%)	10 (1.4%)
CETIRIZINE HYDROCHLORIDE	1 (0.4%)	9 (1.9%)	10 (1.4%)
CINEOLE	3 (1.2%)	7 (1.5%)	10 (1.4%)
CYANOCOBALAMIN	1 (0.4%)	9 (1.9%)	10 (1.4%)
DIHYDROCODEINE BITARTRATE	5 (2.1%)	5 (1.0%)	10 (1.4%)
DILTIAZEM	5 (2.1%)	5 (1.0%)	10 (1.4%)
DIPOTASSIUM CLORAZEPATE	2 (0.8%)	8 (1.7%)	10 (1.4%)
DOMPERIDONE	2 (0.8%)	8 (1.7%)	10 (1.4%)
FAMOTIDINE	3 (1.2%)	7 (1.5%)	10 (1.4%)
GLIMEPIRIDE	3 (1.2%)	7 (1.5%)	10 (1.4%)
LIDOCAINE	3 (1.2%)	7 (1.5%)	10 (1.4%)
PAROXETINE	4 (1.6%)	6 (1.3%)	10 (1.4%)
PERINDOPRIL	3 (1.2%)	7 (1.5%)	10 (1.4%)
PHENYLPROPANOLAMINE HYDROCHLORIDE	5 (2.1%)	5 (1.0%)	10 (1.4%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
RAMIPRIL	1 (0.4%)	9 (1.9%)	10 (1.4%)
SILDENAFIL CITRATE	1 (0.4%)	9 (1.9%)	10 (1.4%)
TETRAZEPAM	2 (0.8%)	8 (1.7%)	10 (1.4%)
VALSARTAN	3 (1.2%)	7 (1.5%)	10 (1.4%)
ALPRAZOLAM	5 (2.1%)	4 (0.8%)	9 (1.2%)
AMILORIDE HYDROCHLORIDE	4 (1.6%)	5 (1.0%)	9 (1.2%)
AMMONIUM CHLORIDE	3 (1.2%)	6 (1.3%)	9 (1.2%)
BENDROFLUMETHIAZIDE	3 (1.2%)	6 (1.3%)	9 (1.2%)
BUFLOMEDIL HYDROCHLORIDE	2 (0.8%)	7 (1.5%)	9 (1.2%)
CARBAMAZEPINE	2 (0.8%)	7 (1.5%)	9 (1.2%)
CEFALEXIN MONOHYDRATE	6 (2.5%)	3 (0.6%)	9 (1.2%)
CEFAZOLIN SODIUM	3 (1.2%)	6 (1.3%)	9 (1.2%)
DEXTROMETHORPHAN HYDROBROMIDE	3 (1.2%)	6 (1.3%)	9 (1.2%)
DIMETICONE	2 (0.8%)	7 (1.5%)	9 (1.2%)
EUCALYPTUS OIL	2 (0.8%)	7 (1.5%)	9 (1.2%)
FEXOFENADINE HYDROCHLORIDE	3 (1.2%)	6 (1.3%)	9 (1.2%)
FLUCONAZOLE	4 (1.6%)	5 (1.0%)	9 (1.2%)
MELOXICAM	5 (2.1%)	4 (0.8%)	9 (1.2%)
NAPROXEN	4 (1.6%)	5 (1.0%)	9 (1.2%)
PHENOXYMETHYLPENICILLIN POTASSIUM	3 (1.2%)	6 (1.3%)	9 (1.2%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
PROPARACETAMOL HYDROCHLORIDE	1 (0.4%)	8 (1.7%)	9 (1.2%)
SULPIRIDE	3 (1.2%)	6 (1.3%)	9 (1.2%)
TORASEMID	4 (1.6%)	5 (1.0%)	9 (1.2%)
AMITRIPTYLINE HYDROCHLORIDE	1 (0.4%)	7 (1.5%)	8 (1.1%)
BELLADONNA EXTRACT	2 (0.8%)	6 (1.3%)	8 (1.1%)
BENZALKONIUM CHLORIDE	4 (1.6%)	4 (0.8%)	8 (1.1%)
BISOPROLOL	1 (0.4%)	7 (1.5%)	8 (1.1%)
BROMPHENIRAMINE MALEATE	7 (2.9%)	1 (0.2%)	8 (1.1%)
CISAPRIDE	1 (0.4%)	7 (1.5%)	8 (1.1%)
CITALOPRAM	3 (1.2%)	5 (1.0%)	8 (1.1%)
CLOTRIMAZOLE	3 (1.2%)	5 (1.0%)	8 (1.1%)
ESTRADIOL	2 (0.8%)	6 (1.3%)	8 (1.1%)
FELODIPINE	4 (1.6%)	4 (0.8%)	8 (1.1%)
HYDROCORTISONE	1 (0.4%)	7 (1.5%)	8 (1.1%)
INDAPAMIDE	1 (0.4%)	7 (1.5%)	8 (1.1%)
MEPROBAMATE	0	8 (1.7%)	8 (1.1%)
MINERALS NOS	4 (1.6%)	4 (0.8%)	8 (1.1%)
MOMETASONE FUROATE	5 (2.1%)	3 (0.6%)	8 (1.1%)
SALICYLIC ACID	3 (1.2%)	5 (1.0%)	8 (1.1%)
TOBRAMYCIN	4 (1.6%)	4 (0.8%)	8 (1.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
TRIPROLIDINE HYDROCHLORIDE	2 (0.8%)	6 (1.3%)	8 (1.1%)
TROXERUTIN	4 (1.6%)	4 (0.8%)	8 (1.1%)
ACICLOVIR	1 (0.4%)	6 (1.3%)	7 (1.0%)
AMFEBUTAMONE	1 (0.4%)	6 (1.3%)	7 (1.0%)
BISACODYL	4 (1.6%)	3 (0.6%)	7 (1.0%)
CALCIUM PANTOTHENATE	3 (1.2%)	4 (0.8%)	7 (1.0%)
CEFOTIAM HEXETIL HYDROCHLORIDE	5 (2.1%)	2 (0.4%)	7 (1.0%)
COLCHICINE	3 (1.2%)	4 (0.8%)	7 (1.0%)
COLECALCIFEROL	3 (1.2%)	4 (0.8%)	7 (1.0%)
EPHEDRINE HYDROCHLORIDE	4 (1.6%)	3 (0.6%)	7 (1.0%)
FERROUS SULFATE	2 (0.8%)	5 (1.0%)	7 (1.0%)
FLUCLOXACILLIN	1 (0.4%)	6 (1.3%)	7 (1.0%)
GLICLAZIDE	2 (0.8%)	5 (1.0%)	7 (1.0%)
HEPTAMINOL HYDROCHLORIDE	3 (1.2%)	4 (0.8%)	7 (1.0%)
HYOSCINE BUTYLBROMIDE	4 (1.6%)	3 (0.6%)	7 (1.0%)
INDOMETACIN	3 (1.2%)	4 (0.8%)	7 (1.0%)
KETOROLAC TROMETHAMINE	4 (1.6%)	3 (0.6%)	7 (1.0%)
METFORMIN	0 .	7 (1.5%)	7 (1.0%)
METOPROLOL SUCCINATE	0 .	7 (1.5%)	7 (1.0%)
NAPHAZOLINE NITRATE	3 (1.2%)	4 (0.8%)	7 (1.0%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
NAPROXEN SODIUM	3 (1.2%)	4 (0.8%)	7 (1.0%)
NORFLOXACIN	1 (0.4%)	6 (1.3%)	7 (1.0%)
OXITROPIUM BROMIDE	4 (1.6%)	3 (0.6%)	7 (1.0%)
PENTOXIFYLLINE	2 (0.8%)	5 (1.0%)	7 (1.0%)
PRAVASTATIN	2 (0.8%)	5 (1.0%)	7 (1.0%)
RIBOFLAVIN	4 (1.6%)	3 (0.6%)	7 (1.0%)
SERENOA REPENS	4 (1.6%)	3 (0.6%)	7 (1.0%)
TIAPROFENIC ACID	3 (1.2%)	4 (0.8%)	7 (1.0%)
TRAMADOL	3 (1.2%)	4 (0.8%)	7 (1.0%)
TRIFLUSAL	3 (1.2%)	4 (0.8%)	7 (1.0%)
ACENOCOUMAROL	0 .	6 (1.3%)	6 (0.8%)
ALENDRONATE	2 (0.8%)	4 (0.8%)	6 (0.8%)
AMINOPHYLLINE	2 (0.8%)	4 (0.8%)	6 (0.8%)
ATENOLOL	3 (1.2%)	3 (0.6%)	6 (0.8%)
ATROPINE SULFATE	3 (1.2%)	3 (0.6%)	6 (0.8%)
ATTAPULGITE	2 (0.8%)	4 (0.8%)	6 (0.8%)
BENZOIC ACID	3 (1.2%)	3 (0.6%)	6 (0.8%)
BUMETANIDE	1 (0.4%)	5 (1.0%)	6 (0.8%)
CAMPHOR	1 (0.4%)	5 (1.0%)	6 (0.8%)
CETRIMONIUM BROMIDE	3 (1.2%)	3 (0.6%)	6 (0.8%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
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SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
DIPHENOXYLATE HYDROCHLORIDE	3 (1.2%)	3 (0.6%)	6 (0.8%)
ERDOSTEINE	4 (1.6%)	2 (0.4%)	6 (0.8%)
FENSPIRIDE HYDROCHLORIDE	2 (0.8%)	4 (0.8%)	6 (0.8%)
FOLIC ACID	1 (0.4%)	5 (1.0%)	6 (0.8%)
GUAIACOL	2 (0.8%)	4 (0.8%)	6 (0.8%)
HEPARIN-FRACTION, SODIUM SALT	1 (0.4%)	5 (1.0%)	6 (0.8%)
LORMETAZEPAM	2 (0.8%)	4 (0.8%)	6 (0.8%)
MAGNESIUM HYDROXIDE	2 (0.8%)	4 (0.8%)	6 (0.8%)
MAGNESIUM NOS	3 (1.2%)	3 (0.6%)	6 (0.8%)
MAGNESIUM OXIDE	2 (0.8%)	4 (0.8%)	6 (0.8%)
METOCLOPRAMIDE HYDROCHLORIDE	2 (0.8%)	4 (0.8%)	6 (0.8%)
MICONAZOLE NITRATE	3 (1.2%)	3 (0.6%)	6 (0.8%)
NICOTINAMIDE	4 (1.6%)	2 (0.4%)	6 (0.8%)
NITRENDIPINE	2 (0.8%)	4 (0.8%)	6 (0.8%)
PHLOROGLUCINOL	2 (0.8%)	4 (0.8%)	6 (0.8%)
PIROXICAM BETA CYCLODEXTRIN	3 (1.2%)	3 (0.6%)	6 (0.8%)
POLYMYXIN B SULFATE	3 (1.2%)	3 (0.6%)	6 (0.8%)
SACCHARIN SODIUM	2 (0.8%)	4 (0.8%)	6 (0.8%)
SACCHAROMYCES BOULARDII	1 (0.4%)	5 (1.0%)	6 (0.8%)
SODIUM CAMSYLATE	2 (0.8%)	4 (0.8%)	6 (0.8%)

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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
SUCRALFATE	2 (0.8%)	4 (0.8%)	6 (0.8%)
TERAZOSIN HYDROCHLORIDE	1 (0.4%)	5 (1.0%)	6 (0.8%)
TETANUS TOXOID	1 (0.4%)	5 (1.0%)	6 (0.8%)
TOLTERODINE	3 (1.2%)	3 (0.6%)	6 (0.8%)
TRIAMCINOLONE	0 .	6 (1.3%)	6 (0.8%)
TRIMETHYLPHLOROGLUCINOL	2 (0.8%)	4 (0.8%)	6 (0.8%)
ALFUZOSIN HYDROCHLORIDE	1 (0.4%)	4 (0.8%)	5 (0.7%)
ALUMINIUM HYDROXIDE-MAGNESIUM CARBONATE	2 (0.8%)	3 (0.6%)	5 (0.7%)
AZELASTINE	2 (0.8%)	3 (0.6%)	5 (0.7%)
BACITRACIN	1 (0.4%)	4 (0.8%)	5 (0.7%)
BENZOCAINE	2 (0.8%)	3 (0.6%)	5 (0.7%)
BEZAFIBRATE	3 (1.2%)	2 (0.4%)	5 (0.7%)
BISOPROLOL FUMARATE	2 (0.8%)	3 (0.6%)	5 (0.7%)
CAFFEINE CITRATE	2 (0.8%)	3 (0.6%)	5 (0.7%)
CANDESARTAN CILEXETIL	1 (0.4%)	4 (0.8%)	5 (0.7%)
CARQUEJA	2 (0.8%)	3 (0.6%)	5 (0.7%)
CEFALEXIN	1 (0.4%)	4 (0.8%)	5 (0.7%)
CEFETAMET	1 (0.4%)	4 (0.8%)	5 (0.7%)
COCARBOXYLASE	1 (0.4%)	4 (0.8%)	5 (0.7%)
DIPHENHYDRAMINE HYDROCHLORIDE	2 (0.8%)	3 (0.6%)	5 (0.7%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
DIPHENYLPYRALINE HYDROCHLORIDE	2 (0.8%)	3 (0.6%)	5 (0.7%)
FENOXAZOLINE HYDROCHLORIDE	2 (0.8%)	3 (0.6%)	5 (0.7%)
FLUOCINOLONE ACETONIDE	1 (0.4%)	4 (0.8%)	5 (0.7%)
FRAMYCETIN SULFATE	0 .	5 (1.0%)	5 (0.7%)
FUSAFUNGINE	1 (0.4%)	4 (0.8%)	5 (0.7%)
GINKGO TREE LEAVES EXTRACT	1 (0.4%)	4 (0.8%)	5 (0.7%)
HEPARIN	0 .	5 (1.0%)	5 (0.7%)
HYDROCORTISONE BUTYRATE	3 (1.2%)	2 (0.4%)	5 (0.7%)
INSULIN HUMAN	0 .	5 (1.0%)	5 (0.7%)
IPECACUANHA	2 (0.8%)	3 (0.6%)	5 (0.7%)
LIQUORICE LIQUID EXTRACT	2 (0.8%)	3 (0.6%)	5 (0.7%)
LOPERAMIDE	1 (0.4%)	4 (0.8%)	5 (0.7%)
LYSOZYME	1 (0.4%)	4 (0.8%)	5 (0.7%)
MESNA	3 (1.2%)	2 (0.4%)	5 (0.7%)
MIKANIA GLOMERATA	2 (0.8%)	3 (0.6%)	5 (0.7%)
NAFTIDROFURYL OXALATE	0 .	5 (1.0%)	5 (0.7%)
NEBIVOLOL HYDROCHLORIDE	2 (0.8%)	3 (0.6%)	5 (0.7%)
NIFLUMIC ACID	2 (0.8%)	3 (0.6%)	5 (0.7%)
NORETHISTERONE ACETATE	1 (0.4%)	4 (0.8%)	5 (0.7%)
PANTOPRAZOL	2 (0.8%)	3 (0.6%)	5 (0.7%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
PAPAIN	1 (0.4%)	4 (0.8%)	5 (0.7%)
PARAFFIN, SOFT	1 (0.4%)	4 (0.8%)	5 (0.7%)
PHENOBARBITAL	2 (0.8%)	3 (0.6%)	5 (0.7%)
PHENYLEPHRINE	3 (1.2%)	2 (0.4%)	5 (0.7%)
PROPYPHENAZONE	1 (0.4%)	4 (0.8%)	5 (0.7%)
PYGEUM AFRICANUM	2 (0.8%)	3 (0.6%)	5 (0.7%)
PYRIDOXINE	1 (0.4%)	4 (0.8%)	5 (0.7%)
REPROTEROL HYDROCHLORIDE	1 (0.4%)	4 (0.8%)	5 (0.7%)
RETINOL	3 (1.2%)	2 (0.4%)	5 (0.7%)
SERTRALINE	0 .	5 (1.0%)	5 (0.7%)
SMECTITE	2 (0.8%)	3 (0.6%)	5 (0.7%)
TEMAZEPAM	1 (0.4%)	4 (0.8%)	5 (0.7%)
TIXOCORTOL PIVALATE	2 (0.8%)	3 (0.6%)	5 (0.7%)
TRANDOLAPRILAT	3 (1.2%)	2 (0.4%)	5 (0.7%)
TRIMETAZIDINE DIHYDROCHLORIDE	1 (0.4%)	4 (0.8%)	5 (0.7%)
TUAMINOHEPTANE SULFATE	2 (0.8%)	3 (0.6%)	5 (0.7%)
VANILLINE	2 (0.8%)	3 (0.6%)	5 (0.7%)
WARFARIN SODIUM	3 (1.2%)	2 (0.4%)	5 (0.7%)
ACARBOSE	2 (0.8%)	2 (0.4%)	4 (0.6%)
ACETAZOLAMIDE	2 (0.8%)	2 (0.4%)	4 (0.6%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
ACETYLDIGOXIN	3 (1.2%)	1 (0.2%)	4 (0.6%)
ALFUZOSIN	2 (0.8%)	2 (0.4%)	4 (0.6%)
AMINOACETIC ACID	2 (0.8%)	2 (0.4%)	4 (0.6%)
AMITRIPTYLINE	1 (0.4%)	3 (0.6%)	4 (0.6%)
AMPHOTERICIN B	2 (0.8%)	2 (0.4%)	4 (0.6%)
ATROPINE BORATE	2 (0.8%)	2 (0.4%)	4 (0.6%)
BRIMONIDINE TARTRATE	0 .	4 (0.8%)	4 (0.6%)
CALCIUM	0 .	4 (0.8%)	4 (0.6%)
CARBOMER	3 (1.2%)	1 (0.2%)	4 (0.6%)
CARVEDILOL	1 (0.4%)	3 (0.6%)	4 (0.6%)
CEFTIBUTEN	1 (0.4%)	3 (0.6%)	4 (0.6%)
CERIVASTATIN	2 (0.8%)	2 (0.4%)	4 (0.6%)
CHLORHEXIDINE GLUCONATE	2 (0.8%)	2 (0.4%)	4 (0.6%)
CHLOROBUTANOL	3 (1.2%)	1 (0.2%)	4 (0.6%)
CIMETIDINE	1 (0.4%)	3 (0.6%)	4 (0.6%)
CLINDAMYCIN HYDROCHLORIDE	2 (0.8%)	2 (0.4%)	4 (0.6%)
CLOBETASONE BUTYRATE	0 .	4 (0.8%)	4 (0.6%)
CROMOGLICATE SODIUM	1 (0.4%)	3 (0.6%)	4 (0.6%)
DEANOL PIDOLATE	3 (1.2%)	1 (0.2%)	4 (0.6%)
DEXCHLORPHENIRAMINE MALEATE	0 .	4 (0.8%)	4 (0.6%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
DIETHYLAMINE SALICYLATE	2 (0.8%)	2 (0.4%)	4 (0.6%)
DIMETICONE, ACTIVATED	2 (0.8%)	2 (0.4%)	4 (0.6%)
DIMETOTIAZINE	2 (0.8%)	2 (0.4%)	4 (0.6%)
DOCUSATE SODIUM	1 (0.4%)	3 (0.6%)	4 (0.6%)
DOXYCYCLINE HYCLATE	2 (0.8%)	2 (0.4%)	4 (0.6%)
EBASTINE	1 (0.4%)	3 (0.6%)	4 (0.6%)
ESTROGENS CONJUGATED	1 (0.4%)	3 (0.6%)	4 (0.6%)
ETHYLENEDIAMINE	2 (0.8%)	2 (0.4%)	4 (0.6%)
FENTANYL	0 .	4 (0.8%)	4 (0.6%)
FLUINDIONE	1 (0.4%)	3 (0.6%)	4 (0.6%)
FUROSEMIDE XANTINOL	3 (1.2%)	1 (0.2%)	4 (0.6%)
FUSIDATE SODIUM	2 (0.8%)	2 (0.4%)	4 (0.6%)
FUSIDIC ACID	2 (0.8%)	2 (0.4%)	4 (0.6%)
GEMFIBROZIL	0 .	4 (0.8%)	4 (0.6%)
GENTAMICIN	1 (0.4%)	3 (0.6%)	4 (0.6%)
GRAMICIDIN	1 (0.4%)	3 (0.6%)	4 (0.6%)
HESPERIDIN METHYL CHALCONE	2 (0.8%)	2 (0.4%)	4 (0.6%)
HEXETIDINE	2 (0.8%)	2 (0.4%)	4 (0.6%)
HYPROMELLOSE	2 (0.8%)	2 (0.4%)	4 (0.6%)
INSULIN INJECTION, ISOPHANE	0 .	4 (0.8%)	4 (0.6%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
MONTELUKAST SODIUM	2 (0.8%)	2 (0.4%)	4 (0.6%)
MONTMORILLONITE BEIDELLITIQUE	3 (1.2%)	1 (0.2%)	4 (0.6%)
MORPHINE	0 .	4 (0.8%)	4 (0.6%)
MULTIVITAMINS, NOS	1 (0.4%)	3 (0.6%)	4 (0.6%)
NIAOULI OIL	2 (0.8%)	2 (0.4%)	4 (0.6%)
NICOTINE	2 (0.8%)	2 (0.4%)	4 (0.6%)
NIMODIPINE	1 (0.4%)	3 (0.6%)	4 (0.6%)
PARAFFIN, LIQUID	1 (0.4%)	3 (0.6%)	4 (0.6%)
PENTOSAN POLYSULFATE	2 (0.8%)	2 (0.4%)	4 (0.6%)
PENTOXYVERINE CITRATE	0 .	4 (0.8%)	4 (0.6%)
POLYVIDONE	1 (0.4%)	3 (0.6%)	4 (0.6%)
POTASSIUM ASCORBATE	1 (0.4%)	3 (0.6%)	4 (0.6%)
PRAVASTATIN SODIUM	3 (1.2%)	1 (0.2%)	4 (0.6%)
PROPOFOL	1 (0.4%)	3 (0.6%)	4 (0.6%)
RAUBASINE	1 (0.4%)	3 (0.6%)	4 (0.6%)
RILMENIDINE PHOSPHATE	2 (0.8%)	2 (0.4%)	4 (0.6%)
RUTOSIDE	0 .	4 (0.8%)	4 (0.6%)
SODIUM LACTATE COMPOUND INJECTION	1 (0.4%)	3 (0.6%)	4 (0.6%)
SOTALOL HYDROCHLORIDE	1 (0.4%)	3 (0.6%)	4 (0.6%)
TELITHROMYCIN	1 (0.4%)	3 (0.6%)	4 (0.6%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
TERPIN HYDRATE	1 (0.4%)	3 (0.6%)	4 (0.6%)
THIOLCHICOSIDE	1 (0.4%)	3 (0.6%)	4 (0.6%)
TIANEPTINE	2 (0.8%)	2 (0.4%)	4 (0.6%)
TOCOPHEROL	2 (0.8%)	2 (0.4%)	4 (0.6%)
VENLAFAXINE	2 (0.8%)	2 (0.4%)	4 (0.6%)
WARFARIN	3 (1.2%)	1 (0.2%)	4 (0.6%)
ACEXAMATE ZINC	1 (0.4%)	2 (0.4%)	3 (0.4%)
ADRENAL CORTICAL EXTRACT	1 (0.4%)	2 (0.4%)	3 (0.4%)
ALMITRINE DIMESILATE	1 (0.4%)	2 (0.4%)	3 (0.4%)
ALTIZIDE	0 .	3 (0.6%)	3 (0.4%)
ALUMINIUM	1 (0.4%)	2 (0.4%)	3 (0.4%)
AMANTADINE HYDROCHLORIDE	2 (0.8%)	1 (0.2%)	3 (0.4%)
AMIKACIN SULFATE	2 (0.8%)	1 (0.2%)	3 (0.4%)
AMIODARONE	0 .	3 (0.6%)	3 (0.4%)
AMOBARBITAL	0 .	3 (0.6%)	3 (0.4%)
AMPICILLIN SODIUM	0 .	3 (0.6%)	3 (0.4%)
ANTIBIOTIC NOS	1 (0.4%)	2 (0.4%)	3 (0.4%)
BACAMPICILLIN HYDROCHLORIDE	0 .	3 (0.6%)	3 (0.4%)
BETAHISTINE HYDROCHLORIDE	2 (0.8%)	1 (0.2%)	3 (0.4%)
BISMUTH	1 (0.4%)	2 (0.4%)	3 (0.4%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
CARBASALATE CALCIUM	1 (0.4%)	2 (0.4%)	3 (0.4%)
CARBIMAZOLE	0 .	3 (0.6%)	3 (0.4%)
CEFONICIDE SODIUM	1 (0.4%)	2 (0.4%)	3 (0.4%)
CELIPROLOL HYDROCHLORIDE	0 .	3 (0.6%)	3 (0.4%)
CHLORTALIDONE	1 (0.4%)	2 (0.4%)	3 (0.4%)
CITRIC ACID	0 .	3 (0.6%)	3 (0.4%)
CLEBOPRIDE	2 (0.8%)	1 (0.2%)	3 (0.4%)
CLEMASTINE FUMARATE	2 (0.8%)	1 (0.2%)	3 (0.4%)
CLONIXIN LYSINATE	2 (0.8%)	1 (0.2%)	3 (0.4%)
CLOXACILLIN SODIUM	1 (0.4%)	2 (0.4%)	3 (0.4%)
CODEINE HYDROCHLORIDE	2 (0.8%)	1 (0.2%)	3 (0.4%)
CYCLOPENTOLATE HYDROCHLORIDE	1 (0.4%)	2 (0.4%)	3 (0.4%)
DALTEPARINE	1 (0.4%)	2 (0.4%)	3 (0.4%)
DESIPRAMINE HYDROCHLORIDE	1 (0.4%)	2 (0.4%)	3 (0.4%)
DEXAMETHASONE SODIUM PHOSPHATE	2 (0.8%)	1 (0.2%)	3 (0.4%)
DIOSMIN	1 (0.4%)	2 (0.4%)	3 (0.4%)
DIPROPHYLLINE	0 .	3 (0.6%)	3 (0.4%)
DORZOLAMIDE HYDROCHLORIDE	0 .	3 (0.6%)	3 (0.4%)
DOSULEPIN	1 (0.4%)	2 (0.4%)	3 (0.4%)
DOXAZOSIN MESYLATE	1 (0.4%)	2 (0.4%)	3 (0.4%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
EMULSIFYING WAX	1 (0.4%)	2 (0.4%)	3 (0.4%)
EPINEPHRINE	1 (0.4%)	2 (0.4%)	3 (0.4%)
ESTRADIOL VALERATE	1 (0.4%)	2 (0.4%)	3 (0.4%)
ETHYLMORPHINE HYDROCHLORIDE	2 (0.8%)	1 (0.2%)	3 (0.4%)
FLUDROCORTISONE ACETATE	2 (0.8%)	1 (0.2%)	3 (0.4%)
FLUNISOLIDE	0 .	3 (0.6%)	3 (0.4%)
FLUNITRAZEPAM	1 (0.4%)	2 (0.4%)	3 (0.4%)
FLUVASTATIN SODIUM	1 (0.4%)	2 (0.4%)	3 (0.4%)
FOSINOPRIL	3 (1.2%)	0 .	3 (0.4%)
GENTIAN	0 .	3 (0.6%)	3 (0.4%)
GLUCOSAMINE	0 .	3 (0.6%)	3 (0.4%)
GLUTAMIC ACID	1 (0.4%)	2 (0.4%)	3 (0.4%)
HALAZEPAM	0 .	3 (0.6%)	3 (0.4%)
HELICIDINE	1 (0.4%)	2 (0.4%)	3 (0.4%)
HEXOPRENALINE SULFATE	2 (0.8%)	1 (0.2%)	3 (0.4%)
HYDROCORTISONE SODIUM PHOSPHATE	1 (0.4%)	2 (0.4%)	3 (0.4%)
HYDROXOCOBALAMIN	2 (0.8%)	1 (0.2%)	3 (0.4%)
HYOSCYAMINE SULFATE	0 .	3 (0.6%)	3 (0.4%)
HYPERICUM EXTRACT	0 .	3 (0.6%)	3 (0.4%)
INOSINE	0 .	3 (0.6%)	3 (0.4%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
INSULIN	1 (0.4%)	2 (0.4%)	3 (0.4%)
ISPAGHULA	1 (0.4%)	2 (0.4%)	3 (0.4%)
KETOCONAZOLE	2 (0.8%)	1 (0.2%)	3 (0.4%)
LACTITOL MONOHYDRATE	2 (0.8%)	1 (0.2%)	3 (0.4%)
LATANOPROST	0 .	3 (0.6%)	3 (0.4%)
LERCANIDIPINE	2 (0.8%)	1 (0.2%)	3 (0.4%)
LEVONORGESTREL	0 .	3 (0.6%)	3 (0.4%)
LYMECYCLINE	1 (0.4%)	2 (0.4%)	3 (0.4%)
MACROGOL	2 (0.8%)	1 (0.2%)	3 (0.4%)
MAGNESIUM CARBONATE	0 .	3 (0.6%)	3 (0.4%)
MAGNESIUM GLUTAMATE	3 (1.2%)	0 .	3 (0.4%)
MEBEVERINE	1 (0.4%)	2 (0.4%)	3 (0.4%)
METOPROLOL	1 (0.4%)	2 (0.4%)	3 (0.4%)
METRONIDAZOLE	1 (0.4%)	2 (0.4%)	3 (0.4%)
MIDAZOLAM MALEATE	3 (1.2%)	0 .	3 (0.4%)
MIZOLASTINE	2 (0.8%)	1 (0.2%)	3 (0.4%)
MOROXYDINE HYDROCHLORIDE	0 .	3 (0.6%)	3 (0.4%)
MORPHINE SULFATE	1 (0.4%)	2 (0.4%)	3 (0.4%)
NIFUROXAZIDE	2 (0.8%)	1 (0.2%)	3 (0.4%)
NITRAZEPAM	1 (0.4%)	2 (0.4%)	3 (0.4%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
OMEPRAZOLE SODIUM	1 (0.4%)	2 (0.4%)	3 (0.4%)
OXAZEPAM	0 .	3 (0.6%)	3 (0.4%)
OXETACAINE	0 .	3 (0.6%)	3 (0.4%)
OXYMETAZOLINE HYDROCHLORIDE	0 .	3 (0.6%)	3 (0.4%)
OXYTETRACYCLINE	2 (0.8%)	1 (0.2%)	3 (0.4%)
OXYTETRACYCLINE CALCIUM	0 .	3 (0.6%)	3 (0.4%)
PANCREATIN	2 (0.8%)	1 (0.2%)	3 (0.4%)
PENTOSAN POLYSULFATE SODIUM	0 .	3 (0.6%)	3 (0.4%)
PHENPROCUMON	1 (0.4%)	2 (0.4%)	3 (0.4%)
PINE OIL	1 (0.4%)	2 (0.4%)	3 (0.4%)
PIRETANIDE	1 (0.4%)	2 (0.4%)	3 (0.4%)
POLYVINYL ALCOHOL	2 (0.8%)	1 (0.2%)	3 (0.4%)
POVIDONE-IODINE	1 (0.4%)	2 (0.4%)	3 (0.4%)
PRAZOSIN	1 (0.4%)	2 (0.4%)	3 (0.4%)
PREDNISOLONE ACETATE	1 (0.4%)	2 (0.4%)	3 (0.4%)
PRIMULA FLOWERS	0 .	3 (0.6%)	3 (0.4%)
PROPRANOLOL	1 (0.4%)	2 (0.4%)	3 (0.4%)
PSEUDOEPHEDRINE	2 (0.8%)	1 (0.2%)	3 (0.4%)
PYRIDOXAL PHOSPHATE	1 (0.4%)	2 (0.4%)	3 (0.4%)
QUININE	1 (0.4%)	2 (0.4%)	3 (0.4%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
QUININE BENZOATE	2 (0.8%)	1 (0.2%)	3 (0.4%)
RUSCUS ACULEATUS	1 (0.4%)	2 (0.4%)	3 (0.4%)
SENNOSIDE A+B	0 .	3 (0.6%)	3 (0.4%)
SODIUM BENZOATE	0 .	3 (0.6%)	3 (0.4%)
SODIUM PHOSPHATE DIBASIC	2 (0.8%)	1 (0.2%)	3 (0.4%)
STERCULIA	0 .	3 (0.6%)	3 (0.4%)
SULFADIAZINE	1 (0.4%)	2 (0.4%)	3 (0.4%)
TERBINAFINE	1 (0.4%)	2 (0.4%)	3 (0.4%)
THIAMINE	1 (0.4%)	2 (0.4%)	3 (0.4%)
THIAMPHENICOL	3 (1.2%)	0 .	3 (0.4%)
THIETHYLPERAZINE MALEATE	2 (0.8%)	1 (0.2%)	3 (0.4%)
TIEMONIUM METHYLSULFATE	0 .	3 (0.6%)	3 (0.4%)
TURPENTINE OIL	1 (0.4%)	2 (0.4%)	3 (0.4%)
VALERIAN ROOT	1 (0.4%)	2 (0.4%)	3 (0.4%)
VENLAFAXINE HYDROCHLORIDE	2 (0.8%)	1 (0.2%)	3 (0.4%)
VERBENA HERB	0 .	3 (0.6%)	3 (0.4%)
ZINC OXIDE	0 .	3 (0.6%)	3 (0.4%)
ACEGLUTAMIDE	0 .	2 (0.4%)	2 (0.3%)
ACETYL ASPARTIC ACID	0 .	2 (0.4%)	2 (0.3%)
ACETYLSALICYLATE CALCIUM	0 .	2 (0.4%)	2 (0.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
ACRIVASTINE	2 (0.8%)	0 .	2 (0.3%)
ALANINE	1 (0.4%)	1 (0.2%)	2 (0.3%)
ALLANTOIN	0 .	2 (0.4%)	2 (0.3%)
ALMASILATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
ALUMINIUM GLYCINATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
ALVERINE CITRATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
AMINO ACIDS NOS	1 (0.4%)	1 (0.2%)	2 (0.3%)
AMPICILLIN	0 .	2 (0.4%)	2 (0.3%)
ASPARTATE MAGNESIUM	0 .	2 (0.4%)	2 (0.3%)
BENSERAZIDE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)
BETAXOLOL	0 .	2 (0.4%)	2 (0.3%)
BETAXOLOL HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)
BEVONIUM METILSULFATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
BROMELAINS	0 .	2 (0.4%)	2 (0.3%)
BUPIVACAINE	0 .	2 (0.4%)	2 (0.3%)
BUTALBITAL	0 .	2 (0.4%)	2 (0.3%)
BUZEPIDE METHYLHYDROXIDE	0 .	2 (0.4%)	2 (0.3%)
CALCIFEDIOL	2 (0.8%)	0 .	2 (0.3%)
CALCITONIN, SALMON	1 (0.4%)	1 (0.2%)	2 (0.3%)
CALCIUM GLUBIONATE	2 (0.8%)	0 .	2 (0.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
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4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
CARBOHYDRATE	0 .	2 (0.4%)	2 (0.3%)
CARRAGENATE	0 .	2 (0.4%)	2 (0.3%)
CEFADROXIL	1 (0.4%)	1 (0.2%)	2 (0.3%)
CEFADROXIL MONOHYDRATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
CEFATRIZINE	1 (0.4%)	1 (0.2%)	2 (0.3%)
CEFAZOLIN	0 .	2 (0.4%)	2 (0.3%)
CEFTAZIDIME	1 (0.4%)	1 (0.2%)	2 (0.3%)
CHLORCYCLIZINE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)
CHLORDIAZEPOXIDE	2 (0.8%)	0 .	2 (0.3%)
CHLORDIAZEPOXIDE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)
CHLORPROMAZINE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)
CIBENZOLINE SUCCINATE	0 .	2 (0.4%)	2 (0.3%)
CINCHOCAINE HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
CINITAPRIDE	0 .	2 (0.4%)	2 (0.3%)
CITRULLINE	0 .	2 (0.4%)	2 (0.3%)
CLINDAMYCIN	0 .	2 (0.4%)	2 (0.3%)
CLOBAZAM	0 .	2 (0.4%)	2 (0.3%)
CLOBETASOL PROPIONATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
CLOMIPRAMINE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)
CLONAZEPAM	0 .	2 (0.4%)	2 (0.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
CLONIDINE HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
COCILLANA LIQUID EXTRACT	2 (0.8%)	0 .	2 (0.3%)
CRATAEGUS	0 .	2 (0.4%)	2 (0.3%)
CYSTINE	0 .	2 (0.4%)	2 (0.3%)
DANTRON	1 (0.4%)	1 (0.2%)	2 (0.3%)
DEXTROMETHORPHAN	1 (0.4%)	1 (0.2%)	2 (0.3%)
DIACEREIN	1 (0.4%)	1 (0.2%)	2 (0.3%)
DICYCLOVERINE HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
DIFLUCORTOLONE VALERATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
DIGITOXIN	1 (0.4%)	1 (0.2%)	2 (0.3%)
DIHYDROCODEINE	2 (0.8%)	0 .	2 (0.3%)
DIHYDROERGOCISTINE MESILATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
DIHYDROERGOTAMINE MESILATE	0 .	2 (0.4%)	2 (0.3%)
DIPYRIDAMOLE	0 .	2 (0.4%)	2 (0.3%)
DOXEPIN	1 (0.4%)	1 (0.2%)	2 (0.3%)
DOXEPIN HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
ECONAZOLE NITRATE	0 .	2 (0.4%)	2 (0.3%)
EMSER SALT	0 .	2 (0.4%)	2 (0.3%)
ESCULIN	1 (0.4%)	1 (0.2%)	2 (0.3%)
ESTRIOL	0 .	2 (0.4%)	2 (0.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
ETHINYLESTRADIOL	0 .	2 (0.4%)	2 (0.3%)
ETILEFRINE HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
FAMCICLOVIR	0 .	2 (0.4%)	2 (0.3%)
FAT	0 .	2 (0.4%)	2 (0.3%)
FINASTERIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
FLECAINIDE ACETATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
FLUNARIZINE DIHYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)
FLUPENTIXOL	1 (0.4%)	1 (0.2%)	2 (0.3%)
FLURAZEPAM HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
GABAPENTIN	0 .	2 (0.4%)	2 (0.3%)
GATIFLOXACIN	0 .	2 (0.4%)	2 (0.3%)
GINSENG	0 .	2 (0.4%)	2 (0.3%)
GLIPIZIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
GLYCEROL	0 .	2 (0.4%)	2 (0.3%)
GOSERELIN	0 .	2 (0.4%)	2 (0.3%)
HALOPERIDOL	0 .	2 (0.4%)	2 (0.3%)
HERBAL EXTRACTS NOS	0 .	2 (0.4%)	2 (0.3%)
HEXAMIDINE ISETHIONATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
HYDROCODONE BITARTRATE	0 .	2 (0.4%)	2 (0.3%)
HYDROCORTISONE ACETATE	0 .	2 (0.4%)	2 (0.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
HYDROXYETHYLCELLULOSE	2 (0.8%)	0 .	2 (0.3%)
IMMUNOGLOBULIN HUMAN NORMAL	2 (0.8%)	0 .	2 (0.3%)
INSULIN HUMAN INJECTION, ISOPHANE	0 .	2 (0.4%)	2 (0.3%)
KETAZOLAM	1 (0.4%)	1 (0.2%)	2 (0.3%)
KETOROLAC	1 (0.4%)	1 (0.2%)	2 (0.3%)
LACIDIPINE	0 .	2 (0.4%)	2 (0.3%)
LACTITOL	0 .	2 (0.4%)	2 (0.3%)
LEVOCABASTINE HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
LEVODOPA	0 .	2 (0.4%)	2 (0.3%)
LOCAL ANESTHESIA	1 (0.4%)	1 (0.2%)	2 (0.3%)
LOPRAZOLAM MESILATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
LORNOXICAM	1 (0.4%)	1 (0.2%)	2 (0.3%)
MAGNESIUM LACTATE	0 .	2 (0.4%)	2 (0.3%)
MAGNESIUM SULFATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
MEBEVERINE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)
MEDAZEPAM	0 .	2 (0.4%)	2 (0.3%)
MELITRACEN	1 (0.4%)	1 (0.2%)	2 (0.3%)
MEPYRAMINE MALEATE	0 .	2 (0.4%)	2 (0.3%)
METFORMIN EMBONATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
METHENAMINE HIPPURATE	1 (0.4%)	1 (0.2%)	2 (0.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
METHIONINE	0 .	2 (0.4%)	2 (0.3%)
METHOTREXATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
METHYL SALICYLATE	0 .	2 (0.4%)	2 (0.3%)
METOPROLOL TARTRATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
MIANSERIN HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
MICONAZOLE	1 (0.4%)	1 (0.2%)	2 (0.3%)
MIGLITOL	0 .	2 (0.4%)	2 (0.3%)
MORPHINE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)
MUCOPOLYSACCHARIDE POLYSULFURIC ACID ESTER	1 (0.4%)	1 (0.2%)	2 (0.3%)
MUPIROCIN	2 (0.8%)	0 .	2 (0.3%)
MYRTILLUS	1 (0.4%)	1 (0.2%)	2 (0.3%)
NABUMETONE	0 .	2 (0.4%)	2 (0.3%)
NICARDIPINE HYDROCHLORIDE	2 (0.8%)	0 .	2 (0.3%)
NICORANDIL	1 (0.4%)	1 (0.2%)	2 (0.3%)
NICOTINE RESIN	1 (0.4%)	1 (0.2%)	2 (0.3%)
NIZATIDINE	1 (0.4%)	1 (0.2%)	2 (0.3%)
NORAMIDOPYRINE METHANESULFONATE MAGNESIUM	1 (0.4%)	1 (0.2%)	2 (0.3%)
NOSCAPINE	1 (0.4%)	1 (0.2%)	2 (0.3%)
NUTRITIONAL SUPPLEMENT NOS	1 (0.4%)	1 (0.2%)	2 (0.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
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INCLUDING CONTINUING PRIOR MEDICATIONS
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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
OINTMENT	2 (0.8%)	0 .	2 (0.3%)
OPIUM	0 .	2 (0.4%)	2 (0.3%)
OXYBUTYNIN	1 (0.4%)	1 (0.2%)	2 (0.3%)
OXYTETRACYCLINE HYDROCHLORIDE	2 (0.8%)	0 .	2 (0.3%)
PANTOPRAZOLE SODIUM	0 .	2 (0.4%)	2 (0.3%)
PAPAVERINE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)
PECTIN	2 (0.8%)	0 .	2 (0.3%)
PENICILLIN NOS	1 (0.4%)	1 (0.2%)	2 (0.3%)
PHENAZONE	0 .	2 (0.4%)	2 (0.3%)
PHENOXYMETHYLPENICILLIN	0 .	2 (0.4%)	2 (0.3%)
PIAS	0 .	2 (0.4%)	2 (0.3%)
PILOCARPINE	0 .	2 (0.4%)	2 (0.3%)
PIPEMIDIC ACID	2 (0.8%)	0 .	2 (0.3%)
POTASSIUM IODIDE	0 .	2 (0.4%)	2 (0.3%)
POTASSIUM MAGNESIUM ASPARTATE	0 .	2 (0.4%)	2 (0.3%)
PRAZOSIN HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
PROPAFENONE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)
PROTEIN	0 .	2 (0.4%)	2 (0.3%)
PRUNUS AFRICANA	1 (0.4%)	1 (0.2%)	2 (0.3%)
PSEUDOEPHEDRINE SULFATE	1 (0.4%)	1 (0.2%)	2 (0.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
QUINAPRIL	2 (0.8%)	0 .	2 (0.3%)
QUINAPRIL HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
QUININE HYDROCHLORIDE	2 (0.8%)	0 .	2 (0.3%)
RABEPRAZOLE SODIUM	1 (0.4%)	1 (0.2%)	2 (0.3%)
REBOXETINE	0 .	2 (0.4%)	2 (0.3%)
RITIOMETAN	0 .	2 (0.4%)	2 (0.3%)
RUMICIS ASETOSA	0 .	2 (0.4%)	2 (0.3%)
SABAL EXTRACT	0 .	2 (0.4%)	2 (0.3%)
SACCHAROSE	0 .	2 (0.4%)	2 (0.3%)
SAMBUCUS FLOWERS	0 .	2 (0.4%)	2 (0.3%)
SENNA	1 (0.4%)	1 (0.2%)	2 (0.3%)
SERINE PHOSPHATE	0 .	2 (0.4%)	2 (0.3%)
SILVER NITRATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
SODIUM PHOSPHATE MONOBASIC	2 (0.8%)	0 .	2 (0.3%)
SPIRAMYCIN	0 .	2 (0.4%)	2 (0.3%)
SULBACTAM	0 .	2 (0.4%)	2 (0.3%)
SULFAFURAZOLE	0 .	2 (0.4%)	2 (0.3%)
SULFOGAIACOL	0 .	2 (0.4%)	2 (0.3%)
TELMISARTAN	1 (0.4%)	1 (0.2%)	2 (0.3%)
TENOXCAM	1 (0.4%)	1 (0.2%)	2 (0.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
TETRYZOLINE HYDROCHLORIDE	2 (0.8%)	0 .	2 (0.3%)
THIAMAZOLE	1 (0.4%)	1 (0.2%)	2 (0.3%)
THIAMINE MONONITRATE	1 (0.4%)	1 (0.2%)	2 (0.3%)
THYROXINE	0 .	2 (0.4%)	2 (0.3%)
TIEMONIUM IODIDE	0 .	2 (0.4%)	2 (0.3%)
TIMOLOL	2 (0.8%)	0 .	2 (0.3%)
TIMOLOL MALEATE	0 .	2 (0.4%)	2 (0.3%)
TITANIUM DIOXIDE	0 .	2 (0.4%)	2 (0.3%)
TOLPERISONE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)
TRANEXAMIC ACID	0 .	2 (0.4%)	2 (0.3%)
TRAZODONE	1 (0.4%)	1 (0.2%)	2 (0.3%)
TRAZODONE HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
TROPICAMIDE	2 (0.8%)	0 .	2 (0.3%)
TROSPIUM CHLORIDE	2 (0.8%)	0 .	2 (0.3%)
UNKNOWN MEDICATION	0 .	2 (0.4%)	2 (0.3%)
URTICA EXTRACT	0 .	2 (0.4%)	2 (0.3%)
VALACYCLOVIR HYDROCHLORIDE	1 (0.4%)	1 (0.2%)	2 (0.3%)
XYLOMETAZOLINE HYDROCHLORIDE	0 .	2 (0.4%)	2 (0.3%)
YEAST DRIED	0 .	2 (0.4%)	2 (0.3%)
ZANAMIVIR	0 .	2 (0.4%)	2 (0.3%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
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4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
ZOLMITRIPTAN	1 (0.4%)	1 (0.2%)	2 (0.3%)
4-AMINO-3-HYDROXYBUTYRIC ACID	0 .	1 (0.2%)	1 (0.1%)
ACAMPROSATE	0 .	1 (0.2%)	1 (0.1%)
ACEPROMAZINE	0 .	1 (0.2%)	1 (0.1%)
ACEPROMETAZINE	0 .	1 (0.2%)	1 (0.1%)
ACETYL-GLUCOSAMINE	0 .	1 (0.2%)	1 (0.1%)
ACONITE TINCTURE	0 .	1 (0.2%)	1 (0.1%)
ADENOSINE PHOSPHATE, SODIUM SALT	0 .	1 (0.2%)	1 (0.1%)
ADENOSINE TRIPHOSPHATE	0 .	1 (0.2%)	1 (0.1%)
ADENOSINE TRIPHOSPHATE, DISODIUM SALT	1 (0.4%)	0 .	1 (0.1%)
ALBUMEN	0 .	1 (0.2%)	1 (0.1%)
ALFACALCIDOL	1 (0.4%)	0 .	1 (0.1%)
ALLERGENIC EXTRACT, NOS	0 .	1 (0.2%)	1 (0.1%)
ALPROSTADIL	0 .	1 (0.2%)	1 (0.1%)
AMANTADINE SULFATE	0 .	1 (0.2%)	1 (0.1%)
AMFEBUTAMONE HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)
AMILORIDE	0 .	1 (0.2%)	1 (0.1%)
AMINOACRIDINE	0 .	1 (0.2%)	1 (0.1%)
AMINOBENZOIC ACID	0 .	1 (0.2%)	1 (0.1%)
AMINOCAPROIC ACID	1 (0.4%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
AMINOHYDROXYPROPYLIDENEDIPHOSPHONATE DISODIUM	1 (0.4%)	0 .	1 (0.1%)
AMINOPENTAMIDE	1 (0.4%)	0 .	1 (0.1%)
AMINOSALICYLIC ACID	0 .	1 (0.2%)	1 (0.1%)
AMISULPRIDE	1 (0.4%)	0 .	1 (0.1%)
AMPICILLIN BENZATHINE	0 .	1 (0.2%)	1 (0.1%)
AMYLASE	1 (0.4%)	0 .	1 (0.1%)
ANALGESICS	0 .	1 (0.2%)	1 (0.1%)
ANESTHESIA, NOS	1 (0.4%)	0 .	1 (0.1%)
ANETHOLE	0 .	1 (0.2%)	1 (0.1%)
ANISATED SPIRIT OF AMMONIA	0 .	1 (0.2%)	1 (0.1%)
ANTAZOLINE SULFATE	0 .	1 (0.2%)	1 (0.1%)
ANTIINFLAMMATORY NOS	0 .	1 (0.2%)	1 (0.1%)
ARACHIS OIL	1 (0.4%)	0 .	1 (0.1%)
ARGININE ASPARTATE	0 .	1 (0.2%)	1 (0.1%)
ASPARTATE POTASSIUM	0 .	1 (0.2%)	1 (0.1%)
ASPARTIC ACID	0 .	1 (0.2%)	1 (0.1%)
ATRACURIUM BESILATE	0 .	1 (0.2%)	1 (0.1%)
AZELASTINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
BACITRACIN ZINC	0 .	1 (0.2%)	1 (0.1%)
BAMBUTEROL HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
BCG VACCINE	1 (0.4%)	0 .	1 (0.1%)
BELLADONNA TINCTURE	0 .	1 (0.2%)	1 (0.1%)
BEMETIZIDE	0 .	1 (0.2%)	1 (0.1%)
BENACTYZINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
BENFLUOREX	1 (0.4%)	0 .	1 (0.1%)
BENFLUOREX HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)
BENFOTIAMINE	0 .	1 (0.2%)	1 (0.1%)
BENZATHINE BENZYL PENICILLIN	0 .	1 (0.2%)	1 (0.1%)
BENZODODECINIUM BROMIDE	1 (0.4%)	0 .	1 (0.1%)
BENZOYL PEROXIDE	0 .	1 (0.2%)	1 (0.1%)
BENZYDAMINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
BENZYL BENZOATE	1 (0.4%)	0 .	1 (0.1%)
BENZYL -P-PHENOL	1 (0.4%)	0 .	1 (0.1%)
BENZYL PENICILLIN SODIUM	0 .	1 (0.2%)	1 (0.1%)
BEPRIDIL HYDROCHLORIDE MONOHYDRATE	0 .	1 (0.2%)	1 (0.1%)
BETACAROTENE	0 .	1 (0.2%)	1 (0.1%)
BETAHISTINE MALEATE	0 .	1 (0.2%)	1 (0.1%)
BIBROCATHOL	0 .	1 (0.2%)	1 (0.1%)
BICALUTAMIDE	1 (0.4%)	0 .	1 (0.1%)
BICLOTYMOL	1 (0.4%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
BIFIDOBACTERIUM BIFIDUM	0 .	1 (0.2%)	1 (0.1%)
BIOFLAVONOIDS	1 (0.4%)	0 .	1 (0.1%)
BIPERIDEN HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
BISMUTH CAMPHOCARBONATE	0 .	1 (0.2%)	1 (0.1%)
BISMUTH SUBCARBONATE	1 (0.4%)	0 .	1 (0.1%)
BORIC ACID	0 .	1 (0.2%)	1 (0.1%)
BROMHEXINE	1 (0.4%)	0 .	1 (0.1%)
BUPIVACAINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
BUSPIRONE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
BUTACAINE SULPHATE	1 (0.4%)	0 .	1 (0.1%)
BUTETAMATE CITRATE	0 .	1 (0.2%)	1 (0.1%)
BUTYLATED HYDROXYANISOLE	0 .	1 (0.2%)	1 (0.1%)
BUTYLATED HYDROXYTOLUENE	0 .	1 (0.2%)	1 (0.1%)
CAJEPUTOL OIL	1 (0.4%)	0 .	1 (0.1%)
CALCIPOTRIOL	0 .	1 (0.2%)	1 (0.1%)
CALCITONIN	1 (0.4%)	0 .	1 (0.1%)
CALCIUM GLUCEPTATE	1 (0.4%)	0 .	1 (0.1%)
CALCIUM GLUCONATE	0 .	1 (0.2%)	1 (0.1%)
CALCIUM PIDOLATE	0 .	1 (0.2%)	1 (0.1%)
CALCIUM POLYSTYRENE SULFONATE	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
CAMPBOR MONOBROMIDE	0 .	1 (0.2%)	1 (0.1%)
CAPSAICIN	0 .	1 (0.2%)	1 (0.1%)
CARBACHOL	0 .	1 (0.2%)	1 (0.1%)
CARBIDOPA	0 .	1 (0.2%)	1 (0.1%)
CARBOHYDRATES NOS	1 (0.4%)	0 .	1 (0.1%)
CARTEOLOL HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)
CEDAR OIL	1 (0.4%)	0 .	1 (0.1%)
CEFAPIRIN SODIUM	1 (0.4%)	0 .	1 (0.1%)
CEFEPIM	0 .	1 (0.2%)	1 (0.1%)
CEFMINOX SODIUM	1 (0.4%)	0 .	1 (0.1%)
CEFONICID DISODIUM	0 .	1 (0.2%)	1 (0.1%)
CEFOTAXIME	1 (0.4%)	0 .	1 (0.1%)
CEFOTIAM	0 .	1 (0.2%)	1 (0.1%)
CEFPIROME SULFATE	0 .	1 (0.2%)	1 (0.1%)
CEFPROZIL MONOHYDRATE	0 .	1 (0.2%)	1 (0.1%)
CEFRADINE	0 .	1 (0.2%)	1 (0.1%)
CETIRIZINE	0 .	1 (0.2%)	1 (0.1%)
CETOMACROGOL	0 .	1 (0.2%)	1 (0.1%)
CETOSTEARYL ALCOHOL	0 .	1 (0.2%)	1 (0.1%)
CETYLPRIDINIUM CHLORIDE	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
CETYLPIRIDINIUM CHLORIDE	0 .	1 (0.2%)	1 (0.1%)
CHAMOMILE	0 .	1 (0.2%)	1 (0.1%)
CHAMOMILE OIL	0 .	1 (0.2%)	1 (0.1%)
CHINOFORM	1 (0.4%)	0 .	1 (0.1%)
CHLORHEXIDINE	1 (0.4%)	0 .	1 (0.1%)
CHLORHEXIDINE DIACETATE	1 (0.4%)	0 .	1 (0.1%)
CHLORHEXIDINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
CHLORINATED LIME AND BORIC ACID SOLUTION	0 .	1 (0.2%)	1 (0.1%)
CHLORMADINONE ACETATE	0 .	1 (0.2%)	1 (0.1%)
CHLORMETHINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
CHLORMEZANONE	0 .	1 (0.2%)	1 (0.1%)
CHLOROFORM AND MORPHINE TINCTURE	1 (0.4%)	0 .	1 (0.1%)
CHLOROPHYLL	1 (0.4%)	0 .	1 (0.1%)
CHLOROQUINE SULFATE	0 .	1 (0.2%)	1 (0.1%)
CHLORPHENAMINE	1 (0.4%)	0 .	1 (0.1%)
CHLORPROPAMIDE	0 .	1 (0.2%)	1 (0.1%)
CHOLINE BITARTRATE	0 .	1 (0.2%)	1 (0.1%)
CHOLINE THEOPHYLLINATE	0 .	1 (0.2%)	1 (0.1%)
CHONDROITIN SULFATE SODIUM	1 (0.4%)	0 .	1 (0.1%)
CICLOPIROX	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
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SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
CIMICIFUGA	0 .	1 (0.2%)	1 (0.1%)
CINITAPRIDE TARTRATE	1 (0.4%)	0 .	1 (0.1%)
CIPROFIBRATE	0 .	1 (0.2%)	1 (0.1%)
CLAVULANATE	0 .	1 (0.2%)	1 (0.1%)
CLEMASTINE	0 .	1 (0.2%)	1 (0.1%)
CLEMIZOLE UNDECYLENATE	1 (0.4%)	0 .	1 (0.1%)
CLIOQUINOL	1 (0.4%)	0 .	1 (0.1%)
CLOBUTINOL HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
CLOCINIZINE	1 (0.4%)	0 .	1 (0.1%)
CLOFOCTOL	1 (0.4%)	0 .	1 (0.1%)
CLOMETOCILLIN POTASSIUM	1 (0.4%)	0 .	1 (0.1%)
CLOPREDNOL	0 .	1 (0.2%)	1 (0.1%)
CLOTIAZEPAM	1 (0.4%)	0 .	1 (0.1%)
COAL TAR SOLUTION	0 .	1 (0.2%)	1 (0.1%)
COUGH COLD PREPARATIONS NOS	0 .	1 (0.2%)	1 (0.1%)
CREATININE SULFATE	1 (0.4%)	0 .	1 (0.1%)
CROTAMITON	0 .	1 (0.2%)	1 (0.1%)
CUCURBITA PEPO	0 .	1 (0.2%)	1 (0.1%)
CYAMEMAZINE	0 .	1 (0.2%)	1 (0.1%)
CYPROHEPTADINE HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
CYPROTERONE ACETATE	1 (0.4%)	0 .	1 (0.1%)
DALTEPARIN SODIUM	1 (0.4%)	0 .	1 (0.1%)
DEOXYRIBONUCLEIC ACID	0 .	1 (0.2%)	1 (0.1%)
DESONIDE	1 (0.4%)	0 .	1 (0.1%)
DESOXIMETASONE	1 (0.4%)	0 .	1 (0.1%)
DEXAMETHASONE ISONICOTINATE	0 .	1 (0.2%)	1 (0.1%)
DEXAMETHASONE SODIUM METASULFOBENZOATE	0 .	1 (0.2%)	1 (0.1%)
DEXCHLORPHENIRAMINE	0 .	1 (0.2%)	1 (0.1%)
DEXPANTHENOL	1 (0.4%)	0 .	1 (0.1%)
DEXTRAN 40	0 .	1 (0.2%)	1 (0.1%)
DEXTROSE PARENTERALS	0 .	1 (0.2%)	1 (0.1%)
DIASTASE	0 .	1 (0.2%)	1 (0.1%)
DIENESTROL	1 (0.4%)	0 .	1 (0.1%)
DIETHANOLAMINE	0 .	1 (0.2%)	1 (0.1%)
DIFEBARBAMATE	0 .	1 (0.2%)	1 (0.1%)
DIHYDROERGOCRYPTINE MESILATE	1 (0.4%)	0 .	1 (0.1%)
DIMEMORFAN PHOSPHATE	1 (0.4%)	0 .	1 (0.1%)
DIMENHYDRINATE	1 (0.4%)	0 .	1 (0.1%)
DIMETINDENE MALEATE	1 (0.4%)	0 .	1 (0.1%)
DISODIUM METHANEARSONATE	1 (0.4%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
DISOPYRAMIDE	1 (0.4%)	0 .	1 (0.1%)
DISOPYRAMIDE PHOSPHATE	0 .	1 (0.2%)	1 (0.1%)
DITAZOLE	0 .	1 (0.2%)	1 (0.1%)
DOCOSAHEXANOIC ACID	0 .	1 (0.2%)	1 (0.1%)
DOXYCYCLINE CALCIUM	1 (0.4%)	0 .	1 (0.1%)
DOXYCYCLINE MONOHYDRATE	0 .	1 (0.2%)	1 (0.1%)
DOXYLAMINE	0 .	1 (0.2%)	1 (0.1%)
DOXYLAMINE SUCCINATE	0 .	1 (0.2%)	1 (0.1%)
EICOSAPENTAENOIC ACID	0 .	1 (0.2%)	1 (0.1%)
ELDER BLOSSOM	0 .	1 (0.2%)	1 (0.1%)
ELECTROLYTES NOS	1 (0.4%)	0 .	1 (0.1%)
EMOLLIENT BASE NOS	0 .	1 (0.2%)	1 (0.1%)
ENOXACIN	0 .	1 (0.2%)	1 (0.1%)
ENOXAPARIN SODIUM	0 .	1 (0.2%)	1 (0.1%)
ENTEROCOCCUS FAECIUM	0 .	1 (0.2%)	1 (0.1%)
EPHEDRINE	0 .	1 (0.2%)	1 (0.1%)
EPHEDRINE SULFATE	0 .	1 (0.2%)	1 (0.1%)
EPRAZINONE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
EPROSARTAN	0 .	1 (0.2%)	1 (0.1%)
ERGOCALCIFEROL	1 (0.4%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
ERGOTAMINE TARTRATE	0 .	1 (0.2%)	1 (0.1%)
ERYSIMUM EXTRACT	0 .	1 (0.2%)	1 (0.1%)
ESCHERICHIA COLI	0 .	1 (0.2%)	1 (0.1%)
ESCIN	1 (0.4%)	0 .	1 (0.1%)
ESOMEPRAZOLE	0 .	1 (0.2%)	1 (0.1%)
ESOMEPRAZOLE MAGNESIUM	1 (0.4%)	0 .	1 (0.1%)
ESSENTIAL OILS NOS	0 .	1 (0.2%)	1 (0.1%)
ESTROGEN NOS	0 .	1 (0.2%)	1 (0.1%)
ETHAMBUTOL DIHYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)
ETHANOL	0 .	1 (0.2%)	1 (0.1%)
ETHENZAMIDE	0 .	1 (0.2%)	1 (0.1%)
ETHYL CHLORIDE	1 (0.4%)	0 .	1 (0.1%)
ETHYL NICOTINATE	1 (0.4%)	0 .	1 (0.1%)
ETHYLMORPHINE	0 .	1 (0.2%)	1 (0.1%)
ETHYLMORPHINE CAMSILATE	0 .	1 (0.2%)	1 (0.1%)
ETIDRONATE DISODIUM	1 (0.4%)	0 .	1 (0.1%)
ETIDRONIC ACID	0 .	1 (0.2%)	1 (0.1%)
ETOFYLLINE	0 .	1 (0.2%)	1 (0.1%)
EUGENOL	0 .	1 (0.2%)	1 (0.1%)
EUPHORBIA	1 (0.4%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
EUPHORBIA LIQUID EXTRACT	1 (0.4%)	0 .	1 (0.1%)
EXPECTORANTS NOS	0 .	1 (0.2%)	1 (0.1%)
EYE MEDICATION, NOS	0 .	1 (0.2%)	1 (0.1%)
FENDILINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
FENOPROFEN CALCIUM	0 .	1 (0.2%)	1 (0.1%)
FENTICONAZOLE NITRATE	0 .	1 (0.2%)	1 (0.1%)
FERROUS FUMARATE	1 (0.4%)	0 .	1 (0.1%)
FLECAINIDE	0 .	1 (0.2%)	1 (0.1%)
FLUMETASONE PIVALATE	1 (0.4%)	0 .	1 (0.1%)
FLUOCORTOLONE	1 (0.4%)	0 .	1 (0.1%)
FLUOCORTOLONE CAPROATE	1 (0.4%)	0 .	1 (0.1%)
FLUOXETINE HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)
FLUPENTIXOL DIHYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
FOSFOMYCIN	0 .	1 (0.2%)	1 (0.1%)
FRANGULA EXTRACT	1 (0.4%)	0 .	1 (0.1%)
FRANGULIN	1 (0.4%)	0 .	1 (0.1%)
GALANTAMINE	0 .	1 (0.2%)	1 (0.1%)
GALLOPAMIL HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)
GLUCOSAMINE SULFATE	0 .	1 (0.2%)	1 (0.1%)
GLUCURONAMIDE	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
GLUTATHIONE	0 .	1 (0.2%)	1 (0.1%)
GLYCOL SALICYLATE	0 .	1 (0.2%)	1 (0.1%)
GLYCOSAMINOGLYCAN POLYSULFATE	0 .	1 (0.2%)	1 (0.1%)
GONADORELIN	1 (0.4%)	0 .	1 (0.1%)
GRAPE SEED	1 (0.4%)	0 .	1 (0.1%)
GREPAFLOXACIN HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)
GRINDELIA	0 .	1 (0.2%)	1 (0.1%)
GRINDELIA LIQUID EXTRACT	0 .	1 (0.2%)	1 (0.1%)
GRISEOFULVIN	0 .	1 (0.2%)	1 (0.1%)
GUANABENZ ACETATE	1 (0.4%)	0 .	1 (0.1%)
HEMATOPORPHYRIN	0 .	1 (0.2%)	1 (0.1%)
HEXACHLOROPHENE	1 (0.4%)	0 .	1 (0.1%)
HEXYL NICOTINATE	1 (0.4%)	0 .	1 (0.1%)
HEXYLRESORCINOL	0 .	1 (0.2%)	1 (0.1%)
HIDROSMIN	0 .	1 (0.2%)	1 (0.1%)
HISTAMINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
HOMATROPINE METHYLBROMIDE	1 (0.4%)	0 .	1 (0.1%)
HYALURONATE SODIUM	1 (0.4%)	0 .	1 (0.1%)
HYALURONIDASE	0 .	1 (0.2%)	1 (0.1%)
HYDROCORTISONE SODIUM SUCCINATE	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
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4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

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SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
HYDROXOCOBALAMIN ACETATE	0 .	1 (0.2%)	1 (0.1%)
HYDROXYCHLOROQUINE SULFATE	0 .	1 (0.2%)	1 (0.1%)
HYPERTONIC SEA WATER SOLUTION	1 (0.4%)	0 .	1 (0.1%)
ICHTHAMMOL	0 .	1 (0.2%)	1 (0.1%)
IMIDUREA	0 .	1 (0.2%)	1 (0.1%)
INOSITOL	0 .	1 (0.2%)	1 (0.1%)
INSULIN PORCINE BASE	0 .	1 (0.2%)	1 (0.1%)
INTRINSIC FACTOR	1 (0.4%)	0 .	1 (0.1%)
IODINE (131 I)	0 .	1 (0.2%)	1 (0.1%)
IPRATROPIUM	0 .	1 (0.2%)	1 (0.1%)
ISOBORNYL ACETATE	0 .	1 (0.2%)	1 (0.1%)
ISONIAZID	1 (0.4%)	0 .	1 (0.1%)
ISOPROMETHAZINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
ISPAGHULA HUSKS	0 .	1 (0.2%)	1 (0.1%)
ITRACONAZOLE	1 (0.4%)	0 .	1 (0.1%)
JOSAMYCIN	0 .	1 (0.2%)	1 (0.1%)
KANAMYCIN SULFATE	1 (0.4%)	0 .	1 (0.1%)
KAOLIN	1 (0.4%)	0 .	1 (0.1%)
KETOBEMIDONE HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)
KETOTIFEN FUMARATE	1 (0.4%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
LACTOBACILLUS ACIDOPHILUS	0 .	1 (0.2%)	1 (0.1%)
LACTOBACILLUS LACTIS	1 (0.4%)	0 .	1 (0.1%)
LACTOSE	0 .	1 (0.2%)	1 (0.1%)
LACTUCA EXTRACT	1 (0.4%)	0 .	1 (0.1%)
LACTUCA SYRUP	1 (0.4%)	0 .	1 (0.1%)
LANOLIN	0 .	1 (0.2%)	1 (0.1%)
LECITHIN	0 .	1 (0.2%)	1 (0.1%)
LEUCOCIANIDOL	1 (0.4%)	0 .	1 (0.1%)
LEVOBUNOLOL HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
LEVOCETIRIZIN DIHYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
LEVODROPROPIZINE	0 .	1 (0.2%)	1 (0.1%)
LEVOGLUTAMIDE	1 (0.4%)	0 .	1 (0.1%)
LEVOMEPRMAZINE MALEATE	1 (0.4%)	0 .	1 (0.1%)
LINCOMYCIN HYDROCHLORIDE MONOHYDRATE	0 .	1 (0.2%)	1 (0.1%)
LINDANE	1 (0.4%)	0 .	1 (0.1%)
LIPIDS NOS	1 (0.4%)	0 .	1 (0.1%)
LIPOPHILER EXTRACT	0 .	1 (0.2%)	1 (0.1%)
LIVER EXTRACTS	0 .	1 (0.2%)	1 (0.1%)
LOFEPRAMINE	0 .	1 (0.2%)	1 (0.1%)
LOFEPRAMINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
LOMEFLOXACIN	1 (0.4%)	0 .	1 (0.1%)
LORACARBEF	0 .	1 (0.2%)	1 (0.1%)
LOSARTAN	1 (0.4%)	0 .	1 (0.1%)
LYCOPUS EUROPAEUS	0 .	1 (0.2%)	1 (0.1%)
MAGALDRATE	1 (0.4%)	0 .	1 (0.1%)
MAGNESIUM ASCORBATE	0 .	1 (0.2%)	1 (0.1%)
MAGNESIUM CHLORIDE	1 (0.4%)	0 .	1 (0.1%)
MAGNESIUM GLUCONATE	1 (0.4%)	0 .	1 (0.1%)
MAGNESIUM GLYCEROPHOSPHATE	1 (0.4%)	0 .	1 (0.1%)
MAGNESIUM LEVULINATE	1 (0.4%)	0 .	1 (0.1%)
MAGNESIUM PIDOLATE	0 .	1 (0.2%)	1 (0.1%)
MAGNESIUM SALT	0 .	1 (0.2%)	1 (0.1%)
MAGNESIUM SPAGLUMINATE	0 .	1 (0.2%)	1 (0.1%)
MAPROTILINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
MARRUBE EXTRACT	0 .	1 (0.2%)	1 (0.1%)
MEDROGESTONE	1 (0.4%)	0 .	1 (0.1%)
MEDROXYPROGESTERONE ACETATE	1 (0.4%)	0 .	1 (0.1%)
MELATONIN	0 .	1 (0.2%)	1 (0.1%)
MELISSA EXTRACT	0 .	1 (0.2%)	1 (0.1%)
MENADIONE	1 (0.4%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
MEQUITAZINE	0 .	1 (0.2%)	1 (0.1%)
MEROPENEM	1 (0.4%)	0 .	1 (0.1%)
METHENAMINE	0 .	1 (0.2%)	1 (0.1%)
METHYLCLOTHIAZIDE	1 (0.4%)	0 .	1 (0.1%)
METHYL NICOTINATE	0 .	1 (0.2%)	1 (0.1%)
METHYLDOPA	0 .	1 (0.2%)	1 (0.1%)
METHYLPARABEN	0 .	1 (0.2%)	1 (0.1%)
METHYLTHIONINIUM CHLORIDE	0 .	1 (0.2%)	1 (0.1%)
METILDIGOXIN	0 .	1 (0.2%)	1 (0.1%)
METOPIMAZINE	1 (0.4%)	0 .	1 (0.1%)
MIANSERIN	0 .	1 (0.2%)	1 (0.1%)
MIDAZOLAM	1 (0.4%)	0 .	1 (0.1%)
MIDECAMYCIN	0 .	1 (0.2%)	1 (0.1%)
MINERAL OIL, LIGHT	0 .	1 (0.2%)	1 (0.1%)
MINOCYCLINE	1 (0.4%)	0 .	1 (0.1%)
MINOCYCLINE HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)
MIOKAMYCIN	0 .	1 (0.2%)	1 (0.1%)
MIRTAZAPINE	1 (0.4%)	0 .	1 (0.1%)
MISTLETOE EXTRACT	0 .	1 (0.2%)	1 (0.1%)
MITOMYCIN	1 (0.4%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
MOCLOBEMIDE	1 (0.4%)	0 .	1 (0.1%)
MOMETASONE	0 .	1 (0.2%)	1 (0.1%)
MUCOPOLYSACCHARIDES	1 (0.4%)	0 .	1 (0.1%)
MULTIMINERALS	1 (0.4%)	0 .	1 (0.1%)
MUPIROCIN CALCIUM	0 .	1 (0.2%)	1 (0.1%)
MYRTECAINE	0 .	1 (0.2%)	1 (0.1%)
MYRTOL	0 .	1 (0.2%)	1 (0.1%)
N, N-DIMETHYL-3, 3-DIPHENYL-1-METHYLALLYLA MINE HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)
NADOLOL	0 .	1 (0.2%)	1 (0.1%)
NEOMYCIN	1 (0.4%)	0 .	1 (0.1%)
NICERGOLINE	0 .	1 (0.2%)	1 (0.1%)
NITROFURANTOIN	1 (0.4%)	0 .	1 (0.1%)
NORDAZEPAM	0 .	1 (0.2%)	1 (0.1%)
NORETHISTERONE	1 (0.4%)	0 .	1 (0.1%)
NOSCAPINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
NSAID, NOS	0 .	1 (0.2%)	1 (0.1%)
NUCLEOTIDES NOS	0 .	1 (0.2%)	1 (0.1%)
NUTMEG OIL	1 (0.4%)	0 .	1 (0.1%)
ONDANSETRON HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
OPIPRAMOL HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040
INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
OPIUM TINCTURE	0 .	1 (0.2%)	1 (0.1%)
ORANGE COLOURING	0 .	1 (0.2%)	1 (0.1%)
ORANGE ESSENCE	0 .	1 (0.2%)	1 (0.1%)
ORLISTAT	1 (0.4%)	0 .	1 (0.1%)
ORNITHINE OXOGLURATE	1 (0.4%)	0 .	1 (0.1%)
OROTIC ACID	0 .	1 (0.2%)	1 (0.1%)
OTILONIUM BROMIDE	1 (0.4%)	0 .	1 (0.1%)
OXACEPROL	1 (0.4%)	0 .	1 (0.1%)
OXOMEMAZINE	0 .	1 (0.2%)	1 (0.1%)
OXYBUTYNIN HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
OXYFEDRINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
PANTHENOL	0 .	1 (0.2%)	1 (0.1%)
PANTOPRAZOLE	1 (0.4%)	0 .	1 (0.1%)
PARADICHLOROBENZENE	1 (0.4%)	0 .	1 (0.1%)
PARAHYDROXYCINNAMIC ACID	0 .	1 (0.2%)	1 (0.1%)
PEMOLINE	1 (0.4%)	0 .	1 (0.1%)
PENCICLOVIR	0 .	1 (0.2%)	1 (0.1%)
PENTETRAZOL	0 .	1 (0.2%)	1 (0.1%)
PENTOBARBITAL	1 (0.4%)	0 .	1 (0.1%)
PEPSIN	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
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4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
PERINDOPRIL ERBUMINE	0 .	1 (0.2%)	1 (0.1%)
PETHIDINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
PHENACETIN	0 .	1 (0.2%)	1 (0.1%)
PHENINDIONE	0 .	1 (0.2%)	1 (0.1%)
PHENIRAMINE AMINOSALICYLATE	0 .	1 (0.2%)	1 (0.1%)
PHENIRAMINE MALEATE	0 .	1 (0.2%)	1 (0.1%)
PHENOBARBITAL CALCIUM	0 .	1 (0.2%)	1 (0.1%)
PHENOXYMETHYLPENICILLIN HYDRABAMINE	0 .	1 (0.2%)	1 (0.1%)
PHENYTOIN	1 (0.4%)	0 .	1 (0.1%)
PHYTOMENADIONE	1 (0.4%)	0 .	1 (0.1%)
PIKETOPROFEN	1 (0.4%)	0 .	1 (0.1%)
PILOCARPINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
PIMPINELLA ROOT	0 .	1 (0.2%)	1 (0.1%)
PINAVERIUM BROMIDE	0 .	1 (0.2%)	1 (0.1%)
PIOGLITAZONE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
PIPERACILLIN	0 .	1 (0.2%)	1 (0.1%)
PIRACETAM	1 (0.4%)	0 .	1 (0.1%)
PIRIBEDIL	1 (0.4%)	0 .	1 (0.1%)
PITOFENONE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
PIVMECILLINAM	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
PIVMECILLINAM HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
POLIOMYELITIS VACCINE INACTIVATED	0 .	1 (0.2%)	1 (0.1%)
POLYGALA AMARA TINCTURE	0 .	1 (0.2%)	1 (0.1%)
POLYGALA SENEGA	1 (0.4%)	0 .	1 (0.1%)
POLYSORBATE 80	1 (0.4%)	0 .	1 (0.1%)
POPULUS EXTRACT	0 .	1 (0.2%)	1 (0.1%)
POPULUS TREMULA	0 .	1 (0.2%)	1 (0.1%)
PRASTERONE	1 (0.4%)	0 .	1 (0.1%)
PREDNICARBATE	0 .	1 (0.2%)	1 (0.1%)
PREDNISOLONE CAPROATE	1 (0.4%)	0 .	1 (0.1%)
PREDNISOLONE-FENOXAZOLINE COMPOUND	0 .	1 (0.2%)	1 (0.1%)
PRIMULA RHIZOME	0 .	1 (0.2%)	1 (0.1%)
PROCAINE	0 .	1 (0.2%)	1 (0.1%)
PROGESTERONE	0 .	1 (0.2%)	1 (0.1%)
PROGUANIL HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
PROMETHAZINE	0 .	1 (0.2%)	1 (0.1%)
PROMETHAZINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
PROPANTHELINE BROMIDE	0 .	1 (0.2%)	1 (0.1%)
PROTEIN HYDROLYSATE	1 (0.4%)	0 .	1 (0.1%)
PROTEINS NOS	1 (0.4%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
PYRAZINAMIDE	1 (0.4%)	0 .	1 (0.1%)
QUEBRACHO BARK	0 .	1 (0.2%)	1 (0.1%)
RAUWOLFIA	0 .	1 (0.2%)	1 (0.1%)
RESCINNAMINE	1 (0.4%)	0 .	1 (0.1%)
RESERPINE	0 .	1 (0.2%)	1 (0.1%)
RETINOL ACETATE	0 .	1 (0.2%)	1 (0.1%)
RIFAMPICIN	1 (0.4%)	0 .	1 (0.1%)
RISEDRONIC ACID MONOSODIUM SALT	0 .	1 (0.2%)	1 (0.1%)
ROCURONIUM	0 .	1 (0.2%)	1 (0.1%)
ROSEMARY OIL	0 .	1 (0.2%)	1 (0.1%)
ROSIGLITAZONE	0 .	1 (0.2%)	1 (0.1%)
ROXATIDINE HYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)
RUSCOGENIN	0 .	1 (0.2%)	1 (0.1%)
RUSCUS ACULEATUS RHIZOME	1 (0.4%)	0 .	1 (0.1%)
SACCHAROMYCES CEREVISIAE	0 .	1 (0.2%)	1 (0.1%)
SALICYLATE SODIUM	0 .	1 (0.2%)	1 (0.1%)
SCOPARIUM	0 .	1 (0.2%)	1 (0.1%)
SELENIUM	0 .	1 (0.2%)	1 (0.1%)
SENNA FRUIT	1 (0.4%)	0 .	1 (0.1%)
SERTRALINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
SEVOFLURANE	0 .	1 (0.2%)	1 (0.1%)
SIBUTRAMINE	0 .	1 (0.2%)	1 (0.1%)
SILICON DIOXIDE, COLLOIDAL	0 .	1 (0.2%)	1 (0.1%)
SITOSTEROLS	1 (0.4%)	0 .	1 (0.1%)
SODIUM AUROTHIOMALATE	1 (0.4%)	0 .	1 (0.1%)
SODIUM BORATE	0 .	1 (0.2%)	1 (0.1%)
SODIUM BROMIDE	0 .	1 (0.2%)	1 (0.1%)
SODIUM CYTIDINE MONOPHOSPHATE	0 .	1 (0.2%)	1 (0.1%)
SODIUM FLUORIDE	0 .	1 (0.2%)	1 (0.1%)
SODIUM LACTATE	1 (0.4%)	0 .	1 (0.1%)
SODIUM MONOMETHYLTRISILANOL ORTHOHYDROXY-BENZOATE	0 .	1 (0.2%)	1 (0.1%)
SODIUM PHOSPHATE	0 .	1 (0.2%)	1 (0.1%)
SODIUM PICOSULFATE	0 .	1 (0.2%)	1 (0.1%)
SODIUM PROPYLPARABEN	0 .	1 (0.2%)	1 (0.1%)
SODIUM SULFATE	0 .	1 (0.2%)	1 (0.1%)
SODIUM SULFATE ANHYDROUS	1 (0.4%)	0 .	1 (0.1%)
SODIUM URIDINE TRIPHOSPHATE	0 .	1 (0.2%)	1 (0.1%)
SOLIDAGO	0 .	1 (0.2%)	1 (0.1%)
SORREL GARDEN HERB	0 .	1 (0.2%)	1 (0.1%)
SOTALOL	1 (0.4%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
SPINAL ANESTHESIA	0 .	1 (0.2%)	1 (0.1%)
SPIRAMYCIN 2	0 .	1 (0.2%)	1 (0.1%)
SQUILL EXTRACT	1 (0.4%)	0 .	1 (0.1%)
SQUILL SYRUP COMPOUND	1 (0.4%)	0 .	1 (0.1%)
STREPTOCOCCUS FAECALIS	0 .	1 (0.2%)	1 (0.1%)
STREPTODORNASE	1 (0.4%)	0 .	1 (0.1%)
STREPTOKINASE	1 (0.4%)	0 .	1 (0.1%)
SUFENTANIL CITRATE	0 .	1 (0.2%)	1 (0.1%)
SULFADIAZINE SILVER	0 .	1 (0.2%)	1 (0.1%)
SULFAMETHIZOLE	1 (0.4%)	0 .	1 (0.1%)
SULFASALAZINE	1 (0.4%)	0 .	1 (0.1%)
SULFATE	1 (0.4%)	0 .	1 (0.1%)
SULFUR	0 .	1 (0.2%)	1 (0.1%)
SULPHANILAMIDE	1 (0.4%)	0 .	1 (0.1%)
SUMATRIPTAN	0 .	1 (0.2%)	1 (0.1%)
TAMOXIFEN	1 (0.4%)	0 .	1 (0.1%)
TAMSULOSIN	1 (0.4%)	0 .	1 (0.1%)
TARTARIC ACID	0 .	1 (0.2%)	1 (0.1%)
TAZOBACTAM	0 .	1 (0.2%)	1 (0.1%)
TERAZOSIN	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
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TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
TERBINAFINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
TERPINEOL	0 .	1 (0.2%)	1 (0.1%)
TESTOSTERONE ENANTATE	1 (0.4%)	0 .	1 (0.1%)
TETANUS ANTITOXIN	1 (0.4%)	0 .	1 (0.1%)
TETRACYCLINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
THIOCTIC ACID	0 .	1 (0.2%)	1 (0.1%)
THIORIDAZINE	1 (0.4%)	0 .	1 (0.1%)
THURFYL SALICYLATE	1 (0.4%)	0 .	1 (0.1%)
THYME EXTRACT	0 .	1 (0.2%)	1 (0.1%)
THYME OIL	0 .	1 (0.2%)	1 (0.1%)
TICARCILLIN DISODIUM	0 .	1 (0.2%)	1 (0.1%)
TICLOPIDINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
TISSUE PLASMINOGEN ACTIVATOR	1 (0.4%)	0 .	1 (0.1%)
TOBRAMYCIN SULFATE	0 .	1 (0.2%)	1 (0.1%)
TOLBUTAMIDE	0 .	1 (0.2%)	1 (0.1%)
TOLFENAMIC ACID	1 (0.4%)	0 .	1 (0.1%)
TOLNAFTATE	1 (0.4%)	0 .	1 (0.1%)
TOPICAL STEROID NOS	0 .	1 (0.2%)	1 (0.1%)
TRAMAZOLINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
TRAPIDIL	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

CONFIDENTIAL

GM2003/00558/00
SB-207499/040

TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
TRETINOIN	1 (0.4%)	0 .	1 (0.1%)
TRIENTINE	0 .	1 (0.2%)	1 (0.1%)
TRIMEBUTINE	0 .	1 (0.2%)	1 (0.1%)
TRIMEBUTINE MALEATE	0 .	1 (0.2%)	1 (0.1%)
TRIMIPRAMINE	0 .	1 (0.2%)	1 (0.1%)
TRIMIPRAMINE MALEATE	0 .	1 (0.2%)	1 (0.1%)
TYROTHRIN	0 .	1 (0.2%)	1 (0.1%)
UBIDECARENONE	1 (0.4%)	0 .	1 (0.1%)
UNDECYLENIC ACID	1 (0.4%)	0 .	1 (0.1%)
URAPIDIL	0 .	1 (0.2%)	1 (0.1%)
URIDINE TRIPHOSPHATE SODIUM	0 .	1 (0.2%)	1 (0.1%)
UROKINASE	0 .	1 (0.2%)	1 (0.1%)
VALERIAN TINCTURE	0 .	1 (0.2%)	1 (0.1%)
VALPROATE SODIUM	0 .	1 (0.2%)	1 (0.1%)
VERALIPRIDE	1 (0.4%)	0 .	1 (0.1%)
VERATROLE	0 .	1 (0.2%)	1 (0.1%)
VILOXAZINE HYDROCHLORIDE	0 .	1 (0.2%)	1 (0.1%)
VINCAMINE	0 .	1 (0.2%)	1 (0.1%)
VIRGAUREA HERB	0 .	1 (0.2%)	1 (0.1%)
VITIS VINIFERA	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.10E

SUMMARY OF COLLAPSED CONCOMITANT MEDICATIONS BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

GENERIC TERM	PLACEBO	PRIOR TREATMENT	Total
	(N=243)	SB 207499 (N=480)	

XIPAMIDE	1 (0.4%)	0 .	1 (0.1%)
ZIPEPROL DIHYDROCHLORIDE	1 (0.4%)	0 .	1 (0.1%)
ZOLPIDEM	1 (0.4%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040
INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

SB 207499

TABLE 13.11A

SUMMARY OF STUDY MEDICATION COMPLIANCE (%) BY PRIOR TREATMENT IN STUDIES 042/091 AND VISIT/WEEK
 PROTOCOL 040

VISIT/WEEK	COMPLIANCE	PLACEBO	PRIOR TREATMENT SB 207499	TOTAL
VISIT 2/WEEK 1	< 80% 80-120% > 120% NUMBER EVALUATED	21 (8.8%) 217 (91.2%) 0 238	32 (6.8%) 436 (93.0%) 1 (0.2%) 469	53 (7.5%) 653 (92.4%) 1 (0.1%) 707
VISIT 3/WEEK 2	< 80% 80-120% > 120% NUMBER EVALUATED	7 (3.0%) 222 (96.5%) 1 (0.4%) 230	5 (1.1%) 453 (98.9%) 0 458	12 (1.7%) 675 (98.1%) 1 (0.1%) 688
VISIT 4/WEEK 4	< 80% 80-120% > 120% NUMBER EVALUATED	4 (1.8%) 215 (98.2%) 0 219	8 (1.7%) 452 (98.3%) 0 460	12 (1.8%) 667 (98.2%) 0 679
VISIT 5/WEEK 8	< 80% 80-120% > 120% NUMBER EVALUATED	5 (2.3%) 209 (97.7%) 0 214	5 (1.1%) 446 (98.7%) 1 (0.2%) 452	10 (1.5%) 655 (98.3%) 1 (0.2%) 666
VISIT 6/WEEK 12	< 80% 80-120% > 120% NUMBER EVALUATED	9 (4.3%) 201 (95.7%) 0 210	11 (2.5%) 433 (97.5%) 0 444	20 (3.1%) 634 (96.9%) 0 654
VISIT 7/WEEK 16	< 80% 80-120% > 120% NUMBER EVALUATED	2 (1.0%) 199 (99.0%) 0 201	4 (0.9%) 431 (98.9%) 1 (0.2%) 436	6 (0.9%) 630 (98.9%) 1 (0.2%) 637
VISIT 8/WEEK 20	< 80% 80-120% > 120% NUMBER EVALUATED	3 (1.5%) 192 (98.5%) 0 195	9 (2.1%) 423 (97.5%) 2 (0.5%) 434	12 (1.9%) 615 (97.8%) 2 (0.3%) 629
VISIT 9/WEEK 24	< 80% 80-120% > 120% NUMBER EVALUATED	3 (1.6%) 189 (98.4%) 0 192	4 (0.9%) 421 (99.1%) 0 425	7 (1.1%) 610 (98.9%) 0 617
VISIT 10/WEEK 28	< 80% 80-120% > 120% NUMBER EVALUATED	3 (1.6%) 186 (98.4%) 0 189	8 (1.9%) 413 (98.1%) 0 421	11 (1.8%) 599 (98.2%) 0 610

1. OVERALL REPRESENTS COMPLIANCE OVER OPEN-LABEL PERIOD

2. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

SB 207499

TABLE 13.11A

SUMMARY OF STUDY MEDICATION COMPLIANCE (%) BY PRIOR TREATMENT IN STUDIES 042/091 AND VISIT/WEEK
 PROTOCOL 040

VISIT/WEEK	COMPLIANCE	PLACEBO	PRIOR TREATMENT SB 207499	TOTAL
VISIT 11/WEEK 32	< 80%	3 (1.6%)	8 (1.9%)	11 (1.8%)
	80-120%	183 (98.4%)	408 (98.1%)	591 (98.2%)
	> 120%	0 .	0 .	0 .
	NUMBER EVALUATED	186	416	602
VISIT 12/WEEK 36	< 80%	4 (2.1%)	6 (1.5%)	10 (1.7%)
	80-120%	183 (97.9%)	401 (98.0%)	584 (98.0%)
	> 120%	0 .	2 (0.5%)	2 (0.3%)
	NUMBER EVALUATED	187	409	596
VISIT 13/WEEK 40	< 80%	2 (1.1%)	5 (1.2%)	7 (1.2%)
	80-120%	184 (98.9%)	395 (98.3%)	579 (98.5%)
	> 120%	0 .	2 (0.5%)	2 (0.3%)
	NUMBER EVALUATED	186	402	588
VISIT 14/WEEK 44	< 80%	3 (1.6%)	13 (3.2%)	16 (2.7%)
	80-120%	180 (98.4%)	387 (96.5%)	567 (97.1%)
	> 120%	0 .	1 (0.2%)	1 (0.2%)
	NUMBER EVALUATED	183	401	584
VISIT 15/WEEK 48	< 80%	5 (2.7%)	3 (0.8%)	8 (1.4%)
	80-120%	178 (97.3%)	396 (99.0%)	574 (98.5%)
	> 120%	0 .	1 (0.3%)	1 (0.2%)
	NUMBER EVALUATED	183	400	583
VISIT 16/WEEK 52	< 80%	2 (1.1%)	6 (1.6%)	8 (1.4%)
	80-120%	173 (98.3%)	378 (97.9%)	551 (98.0%)
	> 120%	1 (0.6%)	2 (0.5%)	3 (0.5%)
	NUMBER EVALUATED	176	386	562
VISIT 17/WEEK 56	< 80%	3 (1.8%)	3 (0.8%)	6 (1.1%)
	80-120%	168 (98.2%)	361 (99.2%)	529 (98.9%)
	> 120%	0 .	0 .	0 .
	NUMBER EVALUATED	171	364	535
VISIT 18/WEEK 60	< 80%	1 (0.6%)	10 (2.7%)	11 (2.0%)
	80-120%	172 (99.4%)	362 (97.1%)	534 (97.8%)
	> 120%	0 .	1 (0.3%)	1 (0.2%)
	NUMBER EVALUATED	173	373	546
VISIT 19/WEEK 64	< 80%	2 (1.4%)	8 (2.6%)	10 (2.2%)
	80-120%	137 (98.6%)	298 (96.8%)	435 (97.3%)
	> 120%	0 .	2 (0.6%)	2 (0.4%)
	NUMBER EVALUATED	139	308	447

1. OVERALL REPRESENTS COMPLIANCE OVER OPEN-LABEL PERIOD

2. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

SB 207499

TABLE 13.11A

SUMMARY OF STUDY MEDICATION COMPLIANCE (%) BY PRIOR TREATMENT IN STUDIES 042/091 AND VISIT/WEEK
 PROTOCOL 040

VISIT/WEEK	COMPLIANCE	PLACEBO	PRIOR TREATMENT SB 207499	TOTAL
VISIT 20/WEEK 68	< 80%	2 (1.4%)	1 (0.3%)	3 (0.7%)
	80-120%	137 (98.6%)	296 (99.3%)	433 (99.1%)
	> 120%	0 .	1 (0.3%)	1 (0.2%)
	NUMBER EVALUATED	139	298	437
VISIT 21/WEEK 72	< 80%	1 (0.6%)	9 (2.5%)	10 (1.9%)
	80-120%	170 (99.4%)	344 (97.2%)	514 (97.9%)
	> 120%	0 .	1 (0.3%)	1 (0.2%)
	NUMBER EVALUATED	171	354	525
VISIT 22/WEEK 76	< 80%	1 (1.0%)	3 (1.5%)	4 (1.4%)
	80-120%	98 (99.0%)	193 (98.5%)	291 (98.6%)
	> 120%	0 .	0 .	0 .
	NUMBER EVALUATED	99	196	295
VISIT 23/WEEK 80	< 80%	1 (1.0%)	1 (0.5%)	2 (0.7%)
	80-120%	95 (99.0%)	188 (99.5%)	283 (99.3%)
	> 120%	0 .	0 .	0 .
	NUMBER EVALUATED	96	189	285
VISIT 24/WEEK 84	< 80%	4 (2.5%)	8 (2.4%)	12 (2.4%)
	80-120%	157 (96.9%)	323 (97.3%)	480 (97.2%)
	> 120%	1 (0.6%)	1 (0.3%)	2 (0.4%)
	NUMBER EVALUATED	162	332	494
VISIT 25/WEEK 88	< 80%	0 .	0 .	0 .
	80-120%	48 (100.0%)	96 (100.0%)	144 (100.0%)
	> 120%	0 .	0 .	0 .
	NUMBER EVALUATED	48	96	144
VISIT 26/WEEK 92	< 80%	1 (2.1%)	0 .	1 (0.7%)
	80-120%	47 (97.9%)	91 (100.0%)	138 (99.3%)
	> 120%	0 .	0 .	0 .
	NUMBER EVALUATED	48	91	139
VISIT 27/WEEK 96	< 80%	5 (3.2%)	10 (3.1%)	15 (3.1%)
	80-120%	146 (94.2%)	312 (96.3%)	458 (95.6%)
	> 120%	4 (2.6%)	2 (0.6%)	6 (1.3%)
	NUMBER EVALUATED	155	324	479
VISIT 28/WEEK 100	< 80%	0 .	0 .	0 .
	80-120%	20 (95.2%)	48 (100.0%)	68 (98.6%)
	> 120%	1 (4.8%)	0 .	1 (1.4%)
	NUMBER EVALUATED	21	48	69

1. OVERALL REPRESENTS COMPLIANCE OVER OPEN-LABEL PERIOD

2. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 13.11A

SUMMARY OF STUDY MEDICATION COMPLIANCE (%) BY PRIOR TREATMENT IN STUDIES 042/091 AND VISIT/WEEK
 PROTOCOL 040

VISIT/WEEK	COMPLIANCE	PLACEBO	PRIOR TREATMENT SB 207499	TOTAL
VISIT 29/WEEK 104	< 80%	0	0	0
	80-120%	17 (100.0%)	40 (100.0%)	57 (100.0%)
	> 120%	0	0	0
	NUMBER EVALUATED	17	40	57
VISIT 30/WEEK 108	< 80%	3 (2.4%)	7 (2.6%)	10 (2.5%)
	80-120%	121 (96.8%)	263 (97.4%)	384 (97.2%)
	> 120%	1 (0.8%)	0	1 (0.3%)
	NUMBER EVALUATED	125	270	395
VISIT 31/WEEK 112	< 80%	0	0	0
	80-120%	9 (100.0%)	18 (100.0%)	27 (100.0%)
	> 120%	0	0	0
	NUMBER EVALUATED	9	18	27
VISIT 32/WEEK 116	< 80%	0	0	0
	80-120%	9 (100.0%)	17 (100.0%)	26 (100.0%)
	> 120%	0	0	0
	NUMBER EVALUATED	9	17	26
VISIT 33/WEEK 120	< 80%	3 (3.4%)	5 (2.6%)	8 (2.9%)
	80-120%	85 (95.5%)	185 (97.4%)	270 (96.8%)
	> 120%	1 (1.1%)	0	1 (0.4%)
	NUMBER EVALUATED	89	190	279
VISIT 34/WEEK 124	< 80%	0	0	0
	80-120%	3 (100.0%)	3 (100.0%)	6 (100.0%)
	> 120%	0	0	0
	NUMBER EVALUATED	3	3	6
VISIT 35/WEEK 128	< 80%	1 (33.3%)	0	1 (16.7%)
	80-120%	2 (66.7%)	3 (100.0%)	5 (83.3%)
	> 120%	0	0	0
	NUMBER EVALUATED	3	3	6
VISIT 36/WEEK 132	< 80%	0	0	0
	80-120%	34 (100.0%)	57 (100.0%)	91 (100.0%)
	> 120%	0	0	0
	NUMBER EVALUATED	34	57	91
VISIT 37/WEEK 136	< 80%	0	0	0
	80-120%	1 (100.0%)	2 (100.0%)	3 (100.0%)
	> 120%	0	0	0
	NUMBER EVALUATED	1	2	3

1. OVERALL REPRESENTS COMPLIANCE OVER OPEN-LABEL PERIOD

2. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 13.11A

SUMMARY OF STUDY MEDICATION COMPLIANCE (%) BY PRIOR TREATMENT IN STUDIES 042/091 AND VISIT/WEEK
PROTOCOL 040

VISIT/WEEK	COMPLIANCE	PLACEBO	PRIOR TREATMENT SB 207499	TOTAL

OVERALL	< 80%	21 (8.6%)	18 (3.8%)	39 (5.4%)
	80-120%	222 (91.4%)	461 (96.2%)	683 (94.6%)
	> 120%	0 .	0 .	0 .
	NUMBER EVALUATED	243	479	722

1. OVERALL REPRESENTS COMPLIANCE OVER OPEN-LABEL PERIOD
2. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

SB 207499

TABLE 13.11B

DESCRIPTIVE STATISTICS FOR STUDY MEDICATION COMPLIANCE (%) BY PRIOR TREATMENT IN STUDIES 042/091 AND VISIT/WEEK
 PROTOCOL 040

VISIT/WEEK	Statistic	PLACEBO (N=243)	Treatment SB 207499 (N=479)	Total (N=722)
VISIT 2/WEEK 1	N	238	469	707
	MEAN	92.45	93.98	93.46
	STD	11.96	12.11	12.07
	MEDIAN	93.75	94.44	93.75
	MIN	28.57	17.86	17.86
	MAX	116.67	137.50	137.50
VISIT 3/WEEK 2	N	230	458	688
	MEAN	97.29	98.07	97.81
	STD	11.40	7.47	8.98
	MEDIAN	100.00	100.00	100.00
	MIN	26.47	7.69	7.69
	MAX	133.33	120.00	133.33
VISIT 4/WEEK 4	N	219	460	679
	MEAN	97.17	97.40	97.32
	STD	8.38	7.52	7.80
	MEDIAN	100.00	100.00	100.00
	MIN	35.71	28.57	28.57
	MAX	118.75	116.67	118.75
VISIT 5/WEEK 8	N	214	452	666
	MEAN	97.04	97.84	97.58
	STD	8.68	7.03	7.60
	MEDIAN	100.00	100.00	100.00
	MIN	0.00	19.64	0.00
	MAX	119.64	120.45	120.45
VISIT 6/WEEK 12	N	210	444	654
	MEAN	96.70	97.13	97.00
	STD	8.88	6.74	7.49
	MEDIAN	100.00	100.00	100.00
	MIN	36.21	27.78	27.78
	MAX	112.50	113.64	113.64
VISIT 7/WEEK 16	N	201	436	637
	MEAN	97.26	97.51	97.43
	STD	5.95	5.18	5.43
	MEDIAN	100.00	100.00	100.00
	MIN	39.71	69.74	39.71
	MAX	106.25	127.27	127.27
VISIT 8/WEEK 20	N	195	434	629
	MEAN	97.49	97.31	97.36

1. OVERALL REPRESENTS COMPLIANCE OVER OPEN-LABEL PERIOD

2. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

SB 207499

TABLE 13.11B

DESCRIPTIVE STATISTICS FOR STUDY MEDICATION COMPLIANCE (%) BY PRIOR TREATMENT IN STUDIES 042/091 AND VISIT/WEEK

PROTOCOL 040

VISIT/WEEK	Statistic	Treatment		Total (N=722)
		PLACEBO (N=243)	SB 207499 (N=479)	
VISIT 8/WEEK 20	STD	6.50	9.76	8.87
	MEDIAN	100.00	100.00	100.00
	MIN	46.83	5.36	5.36
	MAX	110.71	133.33	133.33
VISIT 9/WEEK 24	N	192	425	617
	MEAN	97.55	97.72	97.67
	STD	7.14	4.73	5.59
	MEDIAN	100.00	100.00	100.00
	MIN	43.42	73.08	43.42
VISIT 10/WEEK 28	MAX	117.86	111.36	117.86
	N	189	421	610
	MEAN	97.63	97.54	97.57
	STD	6.69	6.19	6.34
	MEDIAN	100.00	100.00	100.00
VISIT 11/WEEK 32	MIN	44.35	53.13	44.35
	MAX	107.14	118.18	118.18
	N	186	416	602
	MEAN	97.68	97.52	97.57
	STD	5.68	6.27	6.09
VISIT 12/WEEK 36	MEDIAN	100.00	100.00	100.00
	MIN	50.00	46.30	46.30
	MAX	109.52	112.50	112.50
	N	187	409	596
	MEAN	98.17	97.72	97.86
VISIT 13/WEEK 40	STD	5.73	8.62	7.82
	MEDIAN	100.00	100.00	100.00
	MIN	48.21	37.78	37.78
	MAX	112.90	212.50	212.50
	N	186	402	588
VISIT 14/WEEK 44	MEAN	97.94	97.64	97.74
	STD	4.75	6.42	5.94
	MEDIAN	100.00	100.00	100.00
	MIN	74.14	48.28	48.28
	MAX	111.11	132.00	132.00
VISIT 14/WEEK 44	N	183	401	584
	MEAN	97.98	97.13	97.39
	STD	5.91	7.95	7.38
	MEDIAN	100.00	100.00	100.00

1. OVERALL REPRESENTS COMPLIANCE OVER OPEN-LABEL PERIOD

2. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

SB 207499

TABLE 13.11B

DESCRIPTIVE STATISTICS FOR STUDY MEDICATION COMPLIANCE (%) BY PRIOR TREATMENT IN STUDIES 042/091 AND VISIT/WEEK
 PROTOCOL 040

VISIT/WEEK	Statistic	PLACEBO (N=243)	Treatment SB 207499 (N=479)	Total (N=722)
VISIT 14/WEEK 44	MIN	47.30	24.14	24.14
	MAX	117.39	121.74	121.74
VISIT 15/WEEK 48	N	183	400	583
	MEAN	97.15	97.41	97.33
	STD	7.12	6.35	6.60
	MEDIAN	100.00	100.00	100.00
	MIN	50.00	29.17	29.17
	MAX	108.93	130.95	130.95
VISIT 16/WEEK 52	N	176	386	562
	MEAN	97.98	98.03	98.02
	STD	5.97	6.71	6.48
	MEDIAN	100.00	100.00	100.00
	MIN	46.88	46.53	46.53
	MAX	123.33	166.67	166.67
VISIT 17/WEEK 56	N	171	364	535
	MEAN	98.12	97.87	97.95
	STD	6.07	5.58	5.74
	MEDIAN	100.00	100.00	100.00
	MIN	53.57	34.48	34.48
	MAX	106.52	113.64	113.64
VISIT 18/WEEK 60	N	173	373	546
	MEAN	98.22	97.54	97.75
	STD	4.75	5.83	5.52
	MEDIAN	100.00	100.00	100.00
	MIN	78.79	60.71	60.71
	MAX	118.97	128.26	128.26
VISIT 19/WEEK 64	N	139	308	447
	MEAN	97.36	97.66	97.57
	STD	7.18	7.21	7.19
	MEDIAN	100.00	100.00	100.00
	MIN	44.44	48.28	44.44
	MAX	107.69	121.74	121.74
VISIT 20/WEEK 68	N	139	298	437
	MEAN	97.30	97.91	97.72
	STD	7.24	4.71	5.64
	MEDIAN	100.00	100.00	100.00
	MIN	41.84	76.67	41.84
	MAX	106.67	120.83	120.83

1. OVERALL REPRESENTS COMPLIANCE OVER OPEN-LABEL PERIOD

2. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 13.11B

DESCRIPTIVE STATISTICS FOR STUDY MEDICATION COMPLIANCE (%) BY PRIOR TREATMENT IN STUDIES 042/091 AND VISIT/WEEK
 PROTOCOL 040

VISIT/WEEK	Statistic	PLACEBO (N=243)	Treatment SB 207499 (N=479)	Total (N=722)
VISIT 21/WEEK 72	N	171	354	525
	MEAN	97.81	97.16	97.37
	STD	5.03	7.89	7.09
	MEDIAN	100.00	100.00	100.00
	MIN	71.43	41.07	41.07
	MAX	111.29	153.08	153.08
VISIT 22/WEEK 76	N	99	196	295
	MEAN	97.90	97.16	97.41
	STD	6.91	7.46	7.27
	MEDIAN	100.00	100.00	100.00
	MIN	60.71	20.37	20.37
	MAX	116.67	106.82	116.67
VISIT 23/WEEK 80	N	96	189	285
	MEAN	97.63	97.76	97.72
	STD	5.38	4.82	5.01
	MEDIAN	100.00	100.00	100.00
	MIN	79.31	77.63	77.63
	MAX	114.29	112.50	114.29
VISIT 24/WEEK 84	N	162	332	494
	MEAN	98.08	97.54	97.71
	STD	7.69	8.20	8.03
	MEDIAN	100.00	100.00	100.00
	MIN	48.28	27.32	27.32
	MAX	141.89	123.53	141.89
VISIT 25/WEEK 88	N	48	96	144
	MEAN	96.76	97.94	97.54
	STD	5.15	3.74	4.28
	MEDIAN	100.00	100.00	100.00
	MIN	80.00	80.36	80.00
	MAX	101.79	103.03	103.03
VISIT 26/WEEK 92	N	48	91	139
	MEAN	97.23	98.49	98.06
	STD	5.74	4.04	4.71
	MEDIAN	100.00	100.00	100.00
	MIN	78.79	83.33	78.79
	MAX	104.76	112.00	112.00
VISIT 27/WEEK 96	N	156	324	480
	MEAN	99.03	97.37	97.91

1. OVERALL REPRESENTS COMPLIANCE OVER OPEN-LABEL PERIOD

2. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

SB 207499

TABLE 13.11B

DESCRIPTIVE STATISTICS FOR STUDY MEDICATION COMPLIANCE (%) BY PRIOR TREATMENT IN STUDIES 042/091 AND VISIT/WEEK
 PROTOCOL 040

VISIT/WEEK	Statistic	PLACEBO (N=243)	Treatment SB 207499 (N=479)	Total (N=722)
VISIT 27/WEEK 96	STD	27.26	8.85	17.14
	MEDIAN	99.49	99.41	99.45
	MIN	-35.48	7.91	-35.48
	MAX	371.43	136.84	371.43
VISIT 28/WEEK 100	N	21	48	69
	MEAN	117.07	98.57	104.20
	STD	87.81	2.62	48.44
	MEDIAN	100.00	98.64	98.75
	MIN	87.93	91.18	87.93
VISIT 29/WEEK 104	MAX	500.00	103.57	500.00
	N	17	40	57
	MEAN	98.82	98.20	98.39
	STD	2.73	2.16	2.34
	MEDIAN	100.00	98.27	100.00
VISIT 30/WEEK 108	MIN	92.42	93.97	92.42
	MAX	103.13	101.85	103.13
	N	125	270	395
	MEAN	98.63	97.49	97.85
	STD	7.11	5.86	6.29
VISIT 31/WEEK 112	MEDIAN	99.42	98.87	99.19
	MIN	72.47	65.00	65.00
	MAX	142.37	116.46	142.37
	N	9	18	27
	MEAN	97.13	98.92	98.32
VISIT 32/WEEK 116	STD	5.54	6.62	6.23
	MEDIAN	100.00	100.00	100.00
	MIN	83.93	80.36	80.36
	MAX	101.67	113.33	113.33
	N	9	17	26
VISIT 33/WEEK 120	MEAN	97.76	98.35	98.14
	STD	7.56	2.97	4.90
	MEDIAN	100.00	98.28	100.00
	MIN	81.82	92.86	81.82
	MAX	108.93	103.70	108.93
VISIT 33/WEEK 120	N	89	190	279
	MEAN	97.34	96.99	97.10
	STD	9.56	7.60	8.26
	MEDIAN	99.44	98.95	99.32

1. OVERALL REPRESENTS COMPLIANCE OVER OPEN-LABEL PERIOD

2. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 13.11B

DESCRIPTIVE STATISTICS FOR STUDY MEDICATION COMPLIANCE (%) BY PRIOR TREATMENT IN STUDIES 042/091 AND VISIT/WEEK
 PROTOCOL 040

VISIT/WEEK	Statistic	PLACEBO (N=243)	Treatment SB 207499 (N=479)	Total (N=722)
VISIT 33/WEEK 120	MIN	49.40	40.77	40.77
	MAX	136.36	113.79	136.36
VISIT 34/WEEK 124	N	3	3	6
	MEAN	98.67	99.87	99.27
	STD	2.31	3.65	2.81
	MEDIAN	100.00	100.00	100.00
	MIN	96.00	96.15	96.00
	MAX	100.00	103.45	103.45
VISIT 35/WEEK 128	N	3	3	6
	MEAN	92.61	98.81	95.71
	STD	16.85	1.03	11.20
	MEDIAN	96.55	98.28	98.22
	MIN	74.14	98.15	74.14
	MAX	107.14	100.00	107.14
VISIT 36/WEEK 132	N	34	57	91
	MEAN	98.20	98.64	98.48
	STD	3.73	4.83	4.44
	MEDIAN	98.88	99.41	99.40
	MIN	80.95	84.18	80.95
	MAX	102.50	111.69	111.69
VISIT 37/WEEK 136	N	1	2	3
	MEAN	100.00	96.20	97.47
	STD	.	3.58	3.35
	MEDIAN	100.00	96.20	98.73
	MIN	100.00	93.67	93.67
	MAX	100.00	98.73	100.00
OVERALL	N	243	479	722
	MEAN	94.32	95.40	95.03
	STD	12.07	9.73	10.58
	MEDIAN	98.41	98.08	98.16
	MIN	20.00	17.86	17.86
	MAX	108.15	107.14	108.15

1. OVERALL REPRESENTS COMPLIANCE OVER OPEN-LABEL PERIOD

2. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 13.12

SUMMARY OF PATIENT SMOKING STATUS BY BASELINE STATUS, PRIOR TREATMENT IN STUDIES 042/091 AND VISIT/WEEK
 PROTOCOL 040

VISIT/WEEK	PRIOR TREATMENT	BASELINE	-----VISIT STATUS-----				TOTAL
			SMOKING		NOT-SMOKING		
VISIT 1/DAY 1	PLACEBO	SMOKING	83	(89.2%)	10	(10.8%)	93
		NOT-SMOKING	1	(0.7%)	149	(99.3%)	150
		MISSING	0		0		0
		TOTAL	84	(34.6%)	159	(65.4%)	243
	SB 207499	SMOKING	184	(92.9%)	14	(7.1%)	198
		NOT-SMOKING	15	(5.3%)	267	(94.7%)	282
		MISSING	0		0		0
		TOTAL	199	(41.5%)	281	(58.5%)	480
VISIT 2/WEEK 1	PLACEBO	SMOKING	82	(91.1%)	8	(8.9%)	90
		NOT-SMOKING	3	(2.0%)	145	(98.0%)	148
		MISSING	0		0		0
		TOTAL	85	(35.7%)	153	(64.3%)	238
	SB 207499	SMOKING	177	(91.7%)	16	(8.3%)	193
		NOT-SMOKING	13	(4.7%)	263	(95.3%)	276
		MISSING	0		0		0
		TOTAL	190	(40.5%)	279	(59.5%)	469
VISIT 3/WEEK 2	PLACEBO	SMOKING	78	(92.9%)	6	(7.1%)	84
		NOT-SMOKING	2	(1.4%)	143	(98.6%)	145
		MISSING	0		0		0
		TOTAL	80	(34.9%)	149	(65.1%)	229
	SB 207499	SMOKING	172	(91.5%)	16	(8.5%)	188
		NOT-SMOKING	14	(5.1%)	258	(94.9%)	272
		MISSING	0		0		0
		TOTAL	186	(40.4%)	274	(59.6%)	460
VISIT 4/WEEK 4	PLACEBO	SMOKING	74	(90.2%)	8	(9.8%)	82
		NOT-SMOKING	1	(0.7%)	136	(99.3%)	137
		MISSING	0		0		0
		TOTAL	75	(34.2%)	144	(65.8%)	219
	SB 207499	SMOKING	174	(91.6%)	16	(8.4%)	190
		NOT-SMOKING	12	(4.4%)	258	(95.6%)	270
		MISSING	0		0		0
		TOTAL	186	(40.4%)	274	(59.6%)	460
VISIT 5/WEEK 8	PLACEBO	SMOKING	73	(90.1%)	8	(9.9%)	81
		NOT-SMOKING	1	(0.8%)	131	(99.2%)	132
		MISSING	0		0		0

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS EVALUATED AT EACH VISIT

TABLE 13.12

SUMMARY OF PATIENT SMOKING STATUS BY BASELINE STATUS, PRIOR TREATMENT IN STUDIES 042/091 AND VISIT/WEEK
 PROTOCOL 040

VISIT/WEEK	PRIOR TREATMENT	BASELINE	-----VISIT STATUS-----				TOTAL
			SMOKING		NOT-SMOKING		
VISIT 5/WEEK 8	PLACEBO	TOTAL	74	(34.7%)	139	(65.3%)	213
	SB 207499	SMOKING	167	(90.3%)	18	(9.7%)	185
		NOT-SMOKING	12	(4.5%)	255	(95.5%)	267
		MISSING	0		0		0
		TOTAL	179	(39.6%)	273	(60.4%)	452
VISIT 6/WEEK 12	PLACEBO	SMOKING	70	(89.7%)	8	(10.3%)	78
		NOT-SMOKING	1	(0.8%)	129	(99.2%)	130
		MISSING	0		0		0
		TOTAL	71	(34.1%)	137	(65.9%)	208
	SB 207499	SMOKING	161	(88.5%)	21	(11.5%)	182
		NOT-SMOKING	11	(4.2%)	251	(95.8%)	262
		MISSING	0		0		0
		TOTAL	172	(38.7%)	272	(61.3%)	444
		VISIT 7/WEEK 16	PLACEBO	SMOKING	70	(92.1%)	6
NOT-SMOKING	1			(0.8%)	125	(99.2%)	126
MISSING	0				0		0
TOTAL	71			(35.1%)	131	(64.9%)	202
SB 207499	SMOKING		164	(90.6%)	17	(9.4%)	181
	NOT-SMOKING		13	(5.1%)	244	(94.9%)	257
	MISSING		0		0		0
	TOTAL		177	(40.4%)	261	(59.6%)	438
	VISIT 8/WEEK 20		PLACEBO	SMOKING	68	(90.7%)	7
NOT-SMOKING		1		(0.8%)	121	(99.2%)	122
MISSING		0			0		0
TOTAL		69		(35.0%)	128	(65.0%)	197
SB 207499		SMOKING	161	(90.4%)	17	(9.6%)	178
		NOT-SMOKING	13	(5.1%)	244	(94.9%)	257
		MISSING	0		0		0
		TOTAL	174	(40.0%)	261	(60.0%)	435
		VISIT 9/WEEK 24	PLACEBO	SMOKING	66	(91.7%)	6
NOT-SMOKING	2			(1.7%)	119	(98.3%)	121
MISSING	0				0		0
TOTAL	68			(35.2%)	125	(64.8%)	193
SB 207499	SMOKING		159	(90.3%)	17	(9.7%)	176

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS EVALUATED AT EACH VISIT

TABLE 13.12

SUMMARY OF PATIENT SMOKING STATUS BY BASELINE STATUS, PRIOR TREATMENT IN STUDIES 042/091 AND VISIT/WEEK
 PROTOCOL 040

VISIT/WEEK	PRIOR TREATMENT	BASELINE	-----VISIT STATUS-----				TOTAL
			SMOKING		NOT-SMOKING		
VISIT 9/WEEK 24	SB 207499	NOT-SMOKING MISSING TOTAL	12 0 171	(4.8%) (40.0%)	240 0 257	(95.2%) (60.0%)	252 0 428
VISIT 10/WEEK 28	PLACEBO	SMOKING	63	(88.7%)	8	(11.3%)	71
		NOT-SMOKING	2	(1.7%)	118	(98.3%)	120
		MISSING	0		0		0
		TOTAL	65	(34.0%)	126	(66.0%)	191
	SB 207499	SMOKING	153	(87.9%)	21	(12.1%)	174
		NOT-SMOKING MISSING TOTAL	13 0 166	(5.2%) (39.2%)	236 0 257	(94.8%) (60.8%)	249 0 423
VISIT 11/WEEK 32	PLACEBO	SMOKING	61	(87.1%)	9	(12.9%)	70
		NOT-SMOKING	2	(1.7%)	115	(98.3%)	117
		MISSING	0		0		0
		TOTAL	63	(33.7%)	124	(66.3%)	187
	SB 207499	SMOKING	150	(86.7%)	23	(13.3%)	173
		NOT-SMOKING MISSING TOTAL	12 0 162	(4.9%) (38.7%)	234 0 257	(95.1%) (61.3%)	246 0 419
VISIT 12/WEEK 36	PLACEBO	SMOKING	62	(88.6%)	8	(11.4%)	70
		NOT-SMOKING	2	(1.7%)	115	(98.3%)	117
		MISSING	0		0		0
		TOTAL	64	(34.2%)	123	(65.8%)	187
	SB 207499	SMOKING	149	(87.1%)	22	(12.9%)	171
		NOT-SMOKING MISSING TOTAL	11 0 160	(4.5%) (38.7%)	231 0 253	(95.5%) (61.3%)	242 0 413
VISIT 13/WEEK 40	PLACEBO	SMOKING	61	(88.4%)	8	(11.6%)	69
		NOT-SMOKING	2	(1.7%)	114	(98.3%)	116
		MISSING	0		0		0
		TOTAL	63	(34.1%)	122	(65.9%)	185
	SB 207499	SMOKING	149	(88.7%)	19	(11.3%)	168
		NOT-SMOKING MISSING TOTAL	11 0 160	(4.6%) (39.3%)	228 0 247	(95.4%) (60.7%)	239 0 407

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS EVALUATED AT EACH VISIT

TABLE 13.12

SUMMARY OF PATIENT SMOKING STATUS BY BASELINE STATUS, PRIOR TREATMENT IN STUDIES 042/091 AND VISIT/WEEK
 PROTOCOL 040

VISIT/WEEK	PRIOR TREATMENT	BASELINE	-----VISIT STATUS-----				TOTAL
			SMOKING		NOT-SMOKING		
VISIT 14/WEEK 44	PLACEBO	SMOKING	59	(85.5%)	10	(14.5%)	69
		NOT-SMOKING	2	(1.7%)	113	(98.3%)	115
		MISSING	0		0		0
		TOTAL	61	(33.2%)	123	(66.8%)	184
	SB 207499	SMOKING	146	(86.9%)	22	(13.1%)	168
		NOT-SMOKING	13	(5.5%)	225	(94.5%)	238
		MISSING	0		0		0
		TOTAL	159	(39.2%)	247	(60.8%)	406
VISIT 15/WEEK 48	PLACEBO	SMOKING	60	(87.0%)	9	(13.0%)	69
		NOT-SMOKING	3	(2.6%)	112	(97.4%)	115
		MISSING	0		0		0
		TOTAL	63	(34.2%)	121	(65.8%)	184
	SB 207499	SMOKING	144	(86.7%)	22	(13.3%)	166
		NOT-SMOKING	13	(5.5%)	223	(94.5%)	236
		MISSING	0		0		0
		TOTAL	157	(39.1%)	245	(60.9%)	402
VISIT 16/WEEK 52	PLACEBO	SMOKING	61	(89.7%)	7	(10.3%)	68
		NOT-SMOKING	3	(2.7%)	109	(97.3%)	112
		MISSING	0		0		0
		TOTAL	64	(35.6%)	116	(64.4%)	180
	SB 207499	SMOKING	139	(88.0%)	19	(12.0%)	158
		NOT-SMOKING	11	(4.8%)	217	(95.2%)	228
		MISSING	0		0		0
		TOTAL	150	(38.9%)	236	(61.1%)	386
VISIT 17/WEEK 56	PLACEBO	SMOKING	55	(83.3%)	11	(16.7%)	66
		NOT-SMOKING	3	(2.8%)	104	(97.2%)	107
		MISSING	0		0		0
		TOTAL	58	(33.5%)	115	(66.5%)	173
	SB 207499	SMOKING	128	(85.3%)	22	(14.7%)	150
		NOT-SMOKING	10	(4.6%)	207	(95.4%)	217
		MISSING	0		0		0
		TOTAL	138	(37.6%)	229	(62.4%)	367
VISIT 18/WEEK 60	PLACEBO	SMOKING	58	(87.9%)	8	(12.1%)	66
		NOT-SMOKING	3	(2.8%)	105	(97.2%)	108
		MISSING	0		0		0

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS EVALUATED AT EACH VISIT

TABLE 13.12

SUMMARY OF PATIENT SMOKING STATUS BY BASELINE STATUS, PRIOR TREATMENT IN STUDIES 042/091 AND VISIT/WEEK
 PROTOCOL 040

VISIT/WEEK	PRIOR TREATMENT	BASELINE	-----VISIT STATUS-----				TOTAL
			SMOKING		NOT-SMOKING		
VISIT 18/WEEK 60	PLACEBO	TOTAL	61	(35.1%)	113	(64.9%)	174
	SB 207499	SMOKING	131	(85.1%)	23	(14.9%)	154
		NOT-SMOKING	11	(5.0%)	209	(95.0%)	220
		MISSING	0		0		0
		TOTAL	142	(38.0%)	232	(62.0%)	374
VISIT 19/WEEK 64	PLACEBO	SMOKING	44	(83.0%)	9	(17.0%)	53
		NOT-SMOKING	2	(2.2%)	87	(97.8%)	89
		MISSING	0		0		0
		TOTAL	46	(32.4%)	96	(67.6%)	142
	SB 207499	SMOKING	106	(85.5%)	18	(14.5%)	124
		NOT-SMOKING	8	(4.3%)	179	(95.7%)	187
		MISSING	0		0		0
		TOTAL	114	(36.7%)	197	(63.3%)	311
VISIT 20/WEEK 68	PLACEBO	SMOKING	42	(80.8%)	10	(19.2%)	52
		NOT-SMOKING	2	(2.3%)	86	(97.7%)	88
		MISSING	0		0		0
		TOTAL	44	(31.4%)	96	(68.6%)	140
	SB 207499	SMOKING	96	(82.1%)	21	(17.9%)	117
		NOT-SMOKING	7	(3.8%)	176	(96.2%)	183
		MISSING	0		0		0
		TOTAL	103	(34.3%)	197	(65.7%)	300
VISIT 21/WEEK 72	PLACEBO	SMOKING	51	(78.5%)	14	(21.5%)	65
		NOT-SMOKING	2	(1.9%)	104	(98.1%)	106
		MISSING	0		0		0
		TOTAL	53	(31.0%)	118	(69.0%)	171
	SB 207499	SMOKING	121	(83.4%)	24	(16.6%)	145
		NOT-SMOKING	10	(4.7%)	204	(95.3%)	214
		MISSING	0		0		0
		TOTAL	131	(36.5%)	228	(63.5%)	359
VISIT 22/WEEK 76	PLACEBO	SMOKING	27	(77.1%)	8	(22.9%)	35
		NOT-SMOKING	2	(3.1%)	63	(96.9%)	65
		MISSING	0		0		0
		TOTAL	29	(29.0%)	71	(71.0%)	100
	SB 207499	SMOKING	55	(75.3%)	18	(24.7%)	73

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS EVALUATED AT EACH VISIT

TABLE 13.12

SUMMARY OF PATIENT SMOKING STATUS BY BASELINE STATUS, PRIOR TREATMENT IN STUDIES 042/091 AND VISIT/WEEK
 PROTOCOL 040

VISIT/WEEK	PRIOR TREATMENT	BASELINE	-----VISIT STATUS-----				TOTAL
			SMOKING		NOT-SMOKING		
VISIT 22/WEEK 76	SB 207499	NOT-SMOKING	7	(5.6%)	118	(94.4%)	125
		MISSING	0		0		0
		TOTAL	62	(31.3%)	136	(68.7%)	198
VISIT 23/WEEK 80	PLACEBO	SMOKING	25	(71.4%)	10	(28.6%)	35
		NOT-SMOKING	2	(3.1%)	62	(96.9%)	64
		MISSING	0		0		0
	TOTAL	27	(27.3%)	72	(72.7%)	99	
	SB 207499	SMOKING	58	(79.5%)	15	(20.5%)	73
		NOT-SMOKING	7	(5.8%)	113	(94.2%)	120
MISSING		0		0		0	
VISIT 24/WEEK 84	PLACEBO	TOTAL	65	(33.7%)	128	(66.3%)	193
		SMOKING	47	(78.3%)	13	(21.7%)	60
		NOT-SMOKING	2	(1.9%)	101	(98.1%)	103
	MISSING	0		0		0	
	TOTAL	49	(30.1%)	114	(69.9%)	163	
	SB 207499	SMOKING	107	(78.1%)	30	(21.9%)	137
NOT-SMOKING		9	(4.5%)	190	(95.5%)	199	
MISSING		0		0		0	
VISIT 25/WEEK 88	PLACEBO	TOTAL	116	(34.5%)	220	(65.5%)	336
		SMOKING	13	(86.7%)	2	(13.3%)	15
		NOT-SMOKING	2	(5.3%)	36	(94.7%)	38
	MISSING	0		0		0	
	TOTAL	15	(28.3%)	38	(71.7%)	53	
	SB 207499	SMOKING	21	(70.0%)	9	(30.0%)	30
NOT-SMOKING		5	(7.5%)	62	(92.5%)	67	
MISSING		0		0		0	
VISIT 26/WEEK 92	PLACEBO	TOTAL	26	(26.8%)	71	(73.2%)	97
		SMOKING	13	(86.7%)	2	(13.3%)	15
		NOT-SMOKING	2	(5.4%)	35	(94.6%)	37
	MISSING	0		0		0	
	TOTAL	15	(28.8%)	37	(71.2%)	52	
	SB 207499	SMOKING	22	(73.3%)	8	(26.7%)	30
NOT-SMOKING		6	(9.1%)	60	(90.9%)	66	
MISSING		0		0		0	
		TOTAL	28	(29.2%)	68	(70.8%)	96

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS EVALUATED AT EACH VISIT

TABLE 13.12

SUMMARY OF PATIENT SMOKING STATUS BY BASELINE STATUS, PRIOR TREATMENT IN STUDIES 042/091 AND VISIT/WEEK
 PROTOCOL 040

VISIT/WEEK	PRIOR TREATMENT	BASELINE	-----VISIT STATUS-----				TOTAL
			SMOKING		NOT-SMOKING		
VISIT 27/WEEK 96	PLACEBO	SMOKING	47	(78.3%)	13	(21.7%)	60
		NOT-SMOKING	2	(2.0%)	98	(98.0%)	100
		MISSING	0		0		0
		TOTAL	49	(30.6%)	111	(69.4%)	160
	SB 207499	SMOKING	100	(75.8%)	32	(24.2%)	132
		NOT-SMOKING	8	(4.0%)	192	(96.0%)	200
		MISSING	0		0		0
		TOTAL	108	(32.5%)	224	(67.5%)	332
VISIT 28/WEEK 100	PLACEBO	SMOKING	7	(100.0%)	0		7
		NOT-SMOKING	1	(6.7%)	14	(93.3%)	15
		MISSING	0		0		0
		TOTAL	8	(36.4%)	14	(63.6%)	22
	SB 207499	SMOKING	6	(40.0%)	9	(60.0%)	15
		NOT-SMOKING	3	(8.8%)	31	(91.2%)	34
		MISSING	0		0		0
		TOTAL	9	(18.4%)	40	(81.6%)	49
VISIT 29/WEEK 104	PLACEBO	SMOKING	4	(100.0%)	0		4
		NOT-SMOKING	1	(7.1%)	13	(92.9%)	14
		MISSING	0		0		0
		TOTAL	5	(27.8%)	13	(72.2%)	18
	SB 207499	SMOKING	3	(33.3%)	6	(66.7%)	9
		NOT-SMOKING	4	(12.9%)	27	(87.1%)	31
		MISSING	0		0		0
		TOTAL	7	(17.5%)	33	(82.5%)	40
VISIT 30/WEEK 108	PLACEBO	SMOKING	35	(74.5%)	12	(25.5%)	47
		NOT-SMOKING	1	(1.2%)	82	(98.8%)	83
		MISSING	0		0		0
		TOTAL	36	(27.7%)	94	(72.3%)	130
	SB 207499	SMOKING	86	(76.8%)	26	(23.2%)	112
		NOT-SMOKING	8	(4.8%)	157	(95.2%)	165
		MISSING	0		0		0
		TOTAL	94	(33.9%)	183	(66.1%)	277
VISIT 31/WEEK 112	PLACEBO	SMOKING	0		0		0
		NOT-SMOKING	0		9	(100.0%)	9
		MISSING	0		0		0

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS EVALUATED AT EACH VISIT

TABLE 13.12

SUMMARY OF PATIENT SMOKING STATUS BY BASELINE STATUS, PRIOR TREATMENT IN STUDIES 042/091 AND VISIT/WEEK
 PROTOCOL 040

VISIT/WEEK	PRIOR TREATMENT	BASELINE	-----VISIT STATUS-----				TOTAL
			SMOKING		NOT-SMOKING		
VISIT 31/WEEK 112	PLACEBO	TOTAL	0		9	(100.0%)	9
	SB 207499	SMOKING	3	(50.0%)	3	(50.0%)	6
		NOT-SMOKING	1	(8.3%)	11	(91.7%)	12
		MISSING	0		0		0
		TOTAL	4	(22.2%)	14	(77.8%)	18
VISIT 32/WEEK 116	PLACEBO	SMOKING	0		0		0
		NOT-SMOKING	0		9	(100.0%)	9
		MISSING	0		0		0
		TOTAL	0		9	(100.0%)	9
	SB 207499	SMOKING	2	(40.0%)	3	(60.0%)	5
		NOT-SMOKING	1	(8.3%)	11	(91.7%)	12
		MISSING	0		0		0
		TOTAL	3	(17.6%)	14	(82.4%)	17
		VISIT 33/WEEK 120	PLACEBO	SMOKING	20	(62.5%)	12
NOT-SMOKING	1			(1.7%)	58	(98.3%)	59
MISSING	0				0		0
TOTAL	21			(23.1%)	70	(76.9%)	91
SB 207499	SMOKING		60	(77.9%)	17	(22.1%)	77
	NOT-SMOKING	1	(0.9%)	113	(99.1%)	114	
	MISSING	0		0		0	
	TOTAL	61	(31.9%)	130	(68.1%)	191	
VISIT 34/WEEK 124	PLACEBO	SMOKING	0		0		0
		NOT-SMOKING	0		3	(100.0%)	3
		MISSING	0		0		0
		TOTAL	0		3	(100.0%)	3
	SB 207499	SMOKING	0		0		0
		NOT-SMOKING	0		3	(100.0%)	3
		MISSING	0		0		0
		TOTAL	0		3	(100.0%)	3
		VISIT 35/WEEK 128	PLACEBO	SMOKING	0		0
NOT-SMOKING	0				3	(100.0%)	3
MISSING	0				0		0
TOTAL	0				3	(100.0%)	3
SB 207499	SMOKING		0		0		0

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS EVALUATED AT EACH VISIT

TABLE 13.12

SUMMARY OF PATIENT SMOKING STATUS BY BASELINE STATUS, PRIOR TREATMENT IN STUDIES 042/091 AND VISIT/WEEK
 PROTOCOL 040

VISIT/WEEK	PRIOR TREATMENT	BASELINE	-----VISIT STATUS-----				TOTAL	
			SMOKING		NOT-SMOKING			
VISIT 35/WEEK 128	SB 207499	NOT-SMOKING	0		3	(100.0%)	3	
		MISSING	0		0		0	
		TOTAL	0		3	(100.0%)	3	
VISIT 36/WEEK 132	PLACEBO	SMOKING	4	(36.4%)	7	(63.6%)	11	
		NOT-SMOKING	0		25	(100.0%)	25	
		MISSING	0		0		0	
		TOTAL	4	(11.1%)	32	(88.9%)	36	
	SB 207499	SMOKING	13	(65.0%)	7	(35.0%)	20	
		NOT-SMOKING	1	(2.6%)	38	(97.4%)	39	
		MISSING	0		0		0	
		TOTAL	14	(23.7%)	45	(76.3%)	59	
	VISIT 37/WEEK 136	PLACEBO	SMOKING	0		0		0
			NOT-SMOKING	0		1	(100.0%)	1
			MISSING	0		0		0
			TOTAL	0		1	(100.0%)	1
		SB 207499	SMOKING	0		0		0
			NOT-SMOKING	0		2	(100.0%)	2
			MISSING	0		0		0
			TOTAL	0		2	(100.0%)	2
ENDPOINT	PLACEBO	SMOKING	71	(78.0%)	20	(22.0%)	91	
		NOT-SMOKING	2	(1.3%)	147	(98.7%)	149	
		MISSING	0		0		0	
		TOTAL	73	(30.4%)	167	(69.6%)	240	
	SB 207499	SMOKING	157	(80.1%)	39	(19.9%)	196	
		NOT-SMOKING	15	(5.4%)	263	(94.6%)	278	
		MISSING	0		0		0	
		TOTAL	172	(36.3%)	302	(63.7%)	474	

1. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS EVALUATED AT EACH VISIT

SB 207499

TABLE 13.13A

SUMMARY OF CONCOMITANT INHALED CORTICOSTEROID MEDICATIONS
BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
TOTAL	65 (26.7%)	124 (25.8%)	189 (26.1%)
BUDESONIDE	30 (12.3%)	48 (10.0%)	78 (10.8%)
FLUTICASONE PROPIONATE	24 (9.9%)	53 (11.0%)	77 (10.7%)
SALMETEROL XINAFOATE	11 (4.5%)	22 (4.6%)	33 (4.6%)
FLUTICASONE	10 (4.1%)	21 (4.4%)	31 (4.3%)
BECLOMETASONE DIPROPIONATE	9 (3.7%)	12 (2.5%)	21 (2.9%)
SALMETEROL	7 (2.9%)	13 (2.7%)	20 (2.8%)
TRIAMCINOLONE ACETONIDE	4 (1.6%)	10 (2.1%)	14 (1.9%)
FORMOTEROL	4 (1.6%)	5 (1.0%)	9 (1.2%)
MOMETASONE FUROATE	4 (1.6%)	3 (0.6%)	7 (1.0%)
BECLOMETASONE	2 (0.8%)	3 (0.6%)	5 (0.7%)
FLUNISOLIDE	0 .	3 (0.6%)	3 (0.4%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT INHALED CORTICOSTEROID MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

SB 207499

TABLE 13.13B

SUMMARY OF CONCOMITANT ORAL SYSTEMIC CORTICOSTEROID MEDICATIONS GIVEN FOR EXACERBATIONS
BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
TOTAL	66 (27.2%)	133 (27.7%)	199 (27.5%)
PREDNISOLONE	28 (11.5%)	52 (10.8%)	80 (11.1%)
PREDNISONE	23 (9.5%)	43 (9.0%)	66 (9.1%)
METHYLPREDNISOLONE	14 (5.8%)	30 (6.3%)	44 (6.1%)
PREDNISOLONE SODIUM SULFOBENZOATE	10 (4.1%)	20 (4.2%)	30 (4.1%)
DEXAMETHASONE	0 .	3 (0.6%)	3 (0.4%)
PREDNISOLONE ACETATE	0 .	1 (0.2%)	1 (0.1%)
PREDNISOLONE SODIUM SUCCINATE	0 .	1 (0.2%)	1 (0.1%)
TRIAMCINOLONE	0 .	1 (0.2%)	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT ORAL SYSTEMIC CORTICOSTEROID MEDICATION FOR COPD EXACERBATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT COPD EXACERBATION MEDICATION IS DEFINED AS MEDICATION INITIATED ON OR AFTER VISIT 1 OF STUDY 040 AND WHERE THE INDICATION = COPD EXACERBATION
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

TABLE 13.13C

SUMMARY OF CONCOMITANT INHALED ANTICHOLINERGIC MEDICATIONS
BY GENERIC TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

GENERIC TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
TOTAL	120 (49.4%)	224 (46.7%)	344 (47.6%)
IPRATROPIUM BROMIDE	114 (46.9%)	220 (45.8%)	334 (46.2%)
FENOTEROL HYDROBROMIDE	4 (1.6%)	14 (2.9%)	18 (2.5%)
SALBUTAMOL	6 (2.5%)	9 (1.9%)	15 (2.1%)
IPRATROPIUM HYDROXIDE	6 (2.5%)	7 (1.5%)	13 (1.8%)
OXITROPIUM BROMIDE	4 (1.6%)	3 (0.6%)	7 (1.0%)
IPRATROPIUM	0 .	1 (0.2%)	1 (0.1%)
SALBUTAMOL SULFATE	1 (0.4%)	0 .	1 (0.1%)

1. TOTAL ROW REFLECTS TOTAL NUMBER OF PATIENTS RECEIVING CONCOMITANT INHALED ANTICHOLINERGIC MEDICATION
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
3. CONCOMITANT MEDICATIONS DEFINED AS MEDICATION RECEIVED FOLLOWING INITIAL DOSE OF STUDY MEDICATION IN 040 INCLUDING CONTINUING PRIOR MEDICATIONS
4. TABLE IS SORTED BY DESCENDING FREQUENCY OF USE IN THE TOTAL GROUP

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TABLE 14.1A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN FEV1 (L) BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

WEEK	PRIOR TREATMENT	WEEKLY ASSESSMENT						CHANGE FROM BASELINE							
		N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
BASELINE	PLACEBO	232	1.45	0.44	1.40	0.58	3.42	.	.	.	.	.	.	.	.
	SB 207499	469	1.48	0.46	1.41	0.48	3.76	.	.	.	.	.	.	.	.
WEEK 2	PLACEBO	232	1.41	0.44	1.34	0.61	2.54	232	-0.04	0.20	-0.07	-0.01	-0.03	-1.03	0.79
	SB 207499	468	1.48	0.49	1.42	0.53	3.53	468	0.00	0.23	-0.02	0.02	0.01	-0.77	1.82
WEEK 4	PLACEBO	232	1.43	0.45	1.38	0.61	2.81	232	-0.02	0.20	-0.04	0.01	0.00	-0.77	0.85
	SB 207499	468	1.48	0.50	1.40	0.53	3.63	468	0.00	0.23	-0.02	0.02	0.00	-1.00	1.81
WEEK 8	PLACEBO	231	1.43	0.48	1.39	0.53	3.50	231	-0.02	0.20	-0.05	0.01	-0.02	-0.62	0.95
	SB 207499	469	1.49	0.49	1.43	0.57	3.45	469	0.02	0.22	-0.00	0.04	0.02	-0.81	1.53
WEEK 12	PLACEBO	230	1.42	0.45	1.36	0.51	2.98	230	-0.02	0.22	-0.05	0.01	-0.03	-0.70	0.87
	SB 207499	469	1.50	0.51	1.41	0.45	3.49	469	0.02	0.24	0.00	0.04	0.02	-0.74	1.78
WEEK 16	PLACEBO	231	1.43	0.47	1.38	0.50	3.45	231	-0.02	0.23	-0.05	0.01	-0.01	-1.29	1.07
	SB 207499	469	1.51	0.51	1.45	0.44	3.59	469	0.03	0.23	0.01	0.05	0.02	-0.61	1.88
WEEK 20	PLACEBO	232	1.41	0.46	1.33	0.52	3.52	232	-0.03	0.24	-0.06	-0.00	-0.04	-1.28	0.97
	SB 207499	467	1.51	0.52	1.44	0.59	3.69	467	0.03	0.25	0.01	0.06	0.04	-0.75	1.98
WEEK 24	PLACEBO	231	1.41	0.47	1.31	0.60	3.35	231	-0.03	0.24	-0.06	-0.00	-0.01	-1.21	0.80
	SB 207499	468	1.49	0.51	1.44	0.52	3.85	468	0.01	0.26	-0.01	0.04	0.00	-0.61	2.14
WEEK 26	PLACEBO	224	1.41	0.48	1.32	0.52	3.43	224	-0.03	0.24	-0.06	0.00	-0.03	-0.94	0.92
	SB 207499	449	1.49	0.53	1.43	0.45	3.79	449	0.01	0.29	-0.01	0.04	0.00	-0.91	2.08
WEEK 28	PLACEBO	218	1.43	0.49	1.35	0.56	3.40	218	-0.01	0.25	-0.05	0.02	-0.01	-1.23	1.08
	SB 207499	456	1.49	0.52	1.42	0.43	3.90	456	0.01	0.28	-0.02	0.04	0.00	-0.74	2.19
WEEK 32	PLACEBO	212	1.44	0.49	1.37	0.52	3.35	212	-0.01	0.24	-0.04	0.02	-0.01	-1.24	0.99
	SB 207499	449	1.49	0.53	1.42	0.44	3.82	449	0.00	0.28	-0.03	0.03	-0.02	-1.00	2.11
WEEK 36	PLACEBO	206	1.44	0.49	1.38	0.50	3.54	206	-0.01	0.25	-0.04	0.03	-0.02	-0.81	1.04
	SB 207499	442	1.49	0.53	1.43	0.53	3.58	442	0.01	0.29	-0.02	0.03	-0.01	-1.25	1.87
WEEK 40	PLACEBO	202	1.44	0.48	1.34	0.56	3.38	202	-0.01	0.24	-0.04	0.03	-0.01	-1.28	0.99
	SB 207499	434	1.50	0.53	1.44	0.45	3.61	434	0.02	0.27	-0.01	0.04	0.00	-0.90	1.90

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION
4. MAXIMUM OF THREE REPORTED VALUES OF FEV1 IS USED

TABLE 14.1A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN FEV1 (L) BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

		WEEKLY ASSESSMENT						CHANGE FROM BASELINE							
WEEK	PRIOR TREATMENT	N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
WEEK 44	PLACEBO	196	1.44	0.49	1.35	0.46	3.34	196	0.00	0.22	-0.03	0.03	-0.01	-0.65	0.85
	SB 207499	433	1.48	0.52	1.42	0.50	3.65	433	-0.00	0.29	-0.03	0.03	-0.01	-1.20	1.94
WEEK 48	PLACEBO	191	1.44	0.49	1.33	0.54	3.47	191	-0.01	0.24	-0.05	0.02	-0.01	-0.74	0.97
	SB 207499	421	1.48	0.53	1.38	0.43	3.67	421	-0.01	0.28	-0.04	0.02	-0.02	-1.18	1.96
WEEK 52	PLACEBO	188	1.43	0.49	1.31	0.59	3.42	188	-0.02	0.28	-0.06	0.02	0.00	-1.43	1.29
	SB 207499	419	1.47	0.54	1.39	0.38	4.02	419	-0.01	0.30	-0.04	0.02	-0.02	-0.96	2.31
WEEK 56	PLACEBO	185	1.44	0.50	1.35	0.60	3.45	185	-0.01	0.26	-0.05	0.03	-0.01	-1.05	0.90
	SB 207499	409	1.47	0.54	1.39	0.52	3.82	409	-0.01	0.30	-0.04	0.02	-0.02	-1.05	2.11
WEEK 60	PLACEBO	187	1.43	0.48	1.33	0.62	3.44	187	-0.02	0.27	-0.06	0.02	-0.03	-1.66	0.93
	SB 207499	406	1.48	0.53	1.42	0.49	3.80	406	-0.00	0.29	-0.03	0.03	-0.02	-0.93	2.09
WEEK 64	PLACEBO	184	1.42	0.49	1.35	0.53	3.31	184	-0.03	0.26	-0.07	0.01	-0.03	-0.93	0.81
	SB 207499	402	1.47	0.53	1.41	0.48	3.65	402	-0.01	0.29	-0.04	0.02	-0.01	-0.93	1.94
WEEK 68	PLACEBO	182	1.41	0.47	1.34	0.52	3.17	182	-0.04	0.24	-0.08	-0.00	-0.02	-0.99	0.83
	SB 207499	404	1.46	0.53	1.38	0.43	3.60	404	-0.02	0.30	-0.05	0.01	-0.03	-0.91	1.89
WEEK 72	PLACEBO	182	1.41	0.48	1.34	0.49	3.22	182	-0.05	0.28	-0.09	-0.00	-0.04	-1.37	1.03
	SB 207499	397	1.46	0.53	1.39	0.41	3.38	397	-0.02	0.30	-0.05	0.01	-0.04	-1.04	1.67
WEEK 76	PLACEBO	180	1.41	0.51	1.28	0.48	3.27	180	-0.04	0.26	-0.08	-0.00	-0.03	-0.87	1.04
	SB 207499	381	1.44	0.52	1.36	0.45	3.40	381	-0.03	0.29	-0.06	-0.01	-0.05	-0.93	1.32
WEEK 80	PLACEBO	172	1.41	0.49	1.31	0.55	3.18	172	-0.05	0.26	-0.09	-0.01	-0.05	-1.21	0.63
	SB 207499	363	1.44	0.52	1.40	0.35	3.62	363	-0.03	0.30	-0.06	0.00	-0.03	-1.02	1.91
WEEK 84	PLACEBO	174	1.41	0.49	1.33	0.41	3.25	174	-0.04	0.27	-0.08	-0.00	-0.03	-1.19	0.96
	SB 207499	373	1.45	0.53	1.37	0.51	3.49	373	-0.03	0.30	-0.06	0.00	-0.05	-1.15	1.78
WEEK 88	PLACEBO	141	1.39	0.50	1.30	0.40	3.22	141	-0.03	0.25	-0.08	0.01	-0.03	-0.79	0.91
	SB 207499	309	1.42	0.50	1.35	0.45	3.32	309	-0.03	0.28	-0.06	0.00	-0.03	-0.91	1.48
WEEK 92	PLACEBO	140	1.39	0.50	1.31	0.50	3.28	140	-0.04	0.24	-0.08	-0.00	-0.04	-0.67	0.73
	SB 207499	297	1.44	0.56	1.37	0.40	5.51	297	-0.02	0.39	-0.06	0.03	-0.03	-0.86	4.31

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION
4. MAXIMUM OF THREE REPORTED VALUES OF FEV1 IS USED

TABLE 14.1A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN FEV1 (L) BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

WEEK	PRIOR TREATMENT	N	WEEKLY ASSESSMENT					N	CHANGE FROM BASELINE						
			MEAN	STD	MEDIAN	MIN	MAX		MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
WEEK 96	PLACEBO	171	1.40	0.51	1.32	0.52	3.05	171	-0.06	0.27	-0.10	-0.01	-0.06	-1.28	0.90
	SB 207499	357	1.44	0.52	1.37	0.47	3.21	357	-0.05	0.29	-0.08	-0.02	-0.04	-1.03	1.50
WEEK 100	PLACEBO	100	1.38	0.51	1.28	0.57	2.97	100	-0.01	0.25	-0.06	0.03	-0.03	-0.68	0.93
	SB 207499	198	1.36	0.47	1.31	0.50	2.87	198	-0.05	0.27	-0.09	-0.02	-0.04	-0.73	1.19
WEEK 104	PLACEBO	98	1.40	0.53	1.33	0.49	2.84	98	0.00	0.25	-0.05	0.05	0.01	-0.63	1.01
	SB 207499	191	1.37	0.47	1.32	0.47	3.28	191	-0.05	0.29	-0.09	-0.01	-0.03	-1.10	1.17
WEEK 108	PLACEBO	162	1.41	0.52	1.33	0.50	3.19	162	-0.05	0.28	-0.10	-0.01	-0.06	-1.42	1.09
	SB 207499	333	1.43	0.51	1.35	0.57	3.18	333	-0.06	0.30	-0.09	-0.02	-0.05	-0.80	1.41
WEEK 112	PLACEBO	52	1.33	0.46	1.34	0.54	2.38	52	-0.01	0.24	-0.07	0.06	0.00	-0.76	0.51
	SB 207499	95	1.30	0.40	1.26	0.56	2.46	95	-0.08	0.22	-0.13	-0.04	-0.07	-0.62	0.43
WEEK 116	PLACEBO	52	1.37	0.45	1.26	0.55	2.38	52	0.01	0.23	-0.06	0.07	0.06	-0.64	0.39
	SB 207499	93	1.30	0.45	1.24	0.58	2.36	93	-0.07	0.26	-0.13	-0.02	-0.05	-0.81	0.62
WEEK 120	PLACEBO	158	1.40	0.51	1.34	0.49	3.18	158	-0.07	0.32	-0.12	-0.02	-0.05	-1.64	0.96
	SB 207499	327	1.43	0.52	1.36	0.40	3.36	327	-0.05	0.30	-0.08	-0.02	-0.07	-0.95	1.65
WEEK 124	PLACEBO	21	1.34	0.37	1.33	0.61	2.19	21	0.05	0.21	-0.05	0.14	0.01	-0.27	0.49
	SB 207499	48	1.49	0.56	1.37	0.79	3.01	48	0.03	0.34	-0.07	0.13	-0.01	-0.58	1.30
WEEK 128	PLACEBO	17	1.39	0.41	1.34	0.62	2.26	17	0.03	0.23	-0.09	0.14	-0.02	-0.25	0.67
	SB 207499	40	1.41	0.59	1.25	0.54	3.50	40	-0.03	0.34	-0.13	0.08	-0.04	-0.66	1.39
WEEK 132	PLACEBO	129	1.40	0.54	1.32	0.52	3.36	129	-0.09	0.31	-0.14	-0.03	-0.09	-1.06	1.32
	SB 207499	271	1.44	0.52	1.35	0.47	3.19	271	-0.06	0.30	-0.09	-0.02	-0.05	-0.91	1.42
WEEK 136	PLACEBO	9	1.45	0.40	1.32	0.93	2.17	9	0.00	0.25	-0.19	0.19	-0.02	-0.52	0.33
	SB 207499	18	1.23	0.47	1.04	0.56	2.17	18	-0.07	0.24	-0.19	0.06	-0.02	-0.50	0.44
WEEK 140	PLACEBO	9	1.49	0.39	1.31	1.08	2.21	9	0.04	0.20	-0.11	0.20	0.13	-0.31	0.32
	SB 207499	16	1.19	0.44	0.99	0.66	1.96	16	-0.05	0.20	-0.15	0.06	-0.04	-0.37	0.33
WEEK 144	PLACEBO	89	1.38	0.54	1.32	0.51	3.35	89	-0.08	0.31	-0.14	-0.02	-0.09	-0.92	1.31
	SB 207499	187	1.41	0.57	1.30	0.50	3.46	187	-0.04	0.34	-0.09	0.01	-0.07	-1.22	1.75

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION
4. MAXIMUM OF THREE REPORTED VALUES OF FEV1 IS USED

TABLE 14.1A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN FEV1 (L) BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

		WEEKLY ASSESSMENT						CHANGE FROM BASELINE							
WEEK	PRIOR TREATMENT	N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
WEEK 148	PLACEBO SB 207499	3	1.77	0.40	1.75	1.38	2.17	3	0.08	0.23	-0.50	0.66	-0.02	-0.08	0.35
		3	1.30	0.34	1.24	0.99	1.66	3	0.07	0.25	-0.54	0.68	-0.01	-0.12	0.35
WEEK 152	PLACEBO SB 207499	3	1.64	0.56	1.69	1.06	2.18	3	-0.04	0.09	-0.26	0.18	-0.01	-0.14	0.03
		3	1.15	0.33	1.06	0.88	1.52	3	-0.07	0.22	-0.61	0.47	-0.12	-0.26	0.17
WEEK 156	PLACEBO SB 207499	34	1.48	0.64	1.37	0.52	3.73	34	-0.09	0.43	-0.24	0.06	-0.09	-1.24	1.69
		58	1.29	0.49	1.20	0.32	3.09	58	-0.10	0.33	-0.19	-0.01	-0.11	-0.75	1.32
WEEK 160	PLACEBO SB 207499	1	1.73	.	1.73	1.73	1.73	1	-0.10	.	.	.	-0.10	-0.10	-0.10
		2	1.12	0.52	1.12	0.75	1.49	2	-0.27	0.03	-0.52	-0.02	-0.27	-0.29	-0.25
ENDPOINT	PLACEBO SB 207499	232	1.36	0.49	1.28	0.51	3.73	232	-0.09	0.30	-0.12	-0.05	-0.07	-1.24	1.69
		469	1.41	0.51	1.33	0.32	3.46	469	-0.06	0.30	-0.09	-0.03	-0.07	-1.46	1.75

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION
4. MAXIMUM OF THREE REPORTED VALUES OF FEV1 IS USED

TABLE 14.1B

DESCRIPTIVE STATISTICS FOR CHANGE FROM DAY 1 OF STUDY 040 IN FEV1 (L) BY WEEK - PATIENTS RANDOMIZED TO PLACEBO
IN STUDIES 042/091
PROTOCOL 040

WEEKLY ASSESSMENT							CHANGE FROM DAY 1							
WEEK	N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
DAY 1	232	1.42	0.47	1.34	0.61	3.35	.	.	.	.	.	.	.	.
WEEK 2	224	1.41	0.48	1.32	0.52	3.43	224	0.00	0.17	-0.02	0.02	0.00	-0.68	0.63
WEEK 4	218	1.43	0.49	1.35	0.56	3.40	218	0.02	0.18	-0.01	0.04	0.01	-0.72	0.85
WEEK 8	212	1.44	0.49	1.37	0.52	3.35	212	0.02	0.17	-0.00	0.04	0.00	-0.39	0.58
WEEK 12	206	1.44	0.49	1.38	0.50	3.54	206	0.02	0.19	-0.01	0.05	0.02	-0.61	0.55
WEEK 16	202	1.44	0.48	1.34	0.56	3.38	202	0.02	0.19	-0.01	0.05	0.01	-0.43	0.70
WEEK 20	196	1.44	0.49	1.35	0.46	3.34	196	0.02	0.19	-0.00	0.05	0.00	-0.39	0.51
WEEK 24	191	1.44	0.49	1.33	0.54	3.47	191	0.01	0.19	-0.02	0.04	0.01	-0.55	0.62
WEEK 28	188	1.43	0.49	1.31	0.59	3.42	188	0.00	0.20	-0.03	0.03	-0.00	-0.70	0.67
WEEK 32	185	1.44	0.50	1.35	0.60	3.45	185	0.02	0.19	-0.01	0.04	0.01	-0.58	0.63
WEEK 36	187	1.43	0.48	1.33	0.62	3.44	187	0.01	0.21	-0.02	0.03	0.01	-0.67	0.72
WEEK 40	184	1.42	0.49	1.35	0.53	3.31	184	-0.00	0.22	-0.04	0.03	-0.02	-0.69	0.80
WEEK 44	182	1.41	0.47	1.34	0.52	3.17	182	-0.02	0.20	-0.05	0.01	-0.03	-0.89	0.82
WEEK 48	182	1.41	0.48	1.34	0.49	3.22	182	-0.02	0.22	-0.05	0.01	-0.01	-0.74	0.91
WEEK 52	180	1.41	0.51	1.28	0.48	3.27	180	-0.02	0.22	-0.05	0.01	-0.02	-0.63	0.90
WEEK 56	172	1.41	0.49	1.31	0.55	3.18	172	-0.02	0.22	-0.06	0.01	-0.03	-0.66	0.76
WEEK 60	174	1.41	0.49	1.33	0.41	3.25	174	-0.02	0.23	-0.05	0.02	-0.03	-0.59	0.77
WEEK 64	141	1.39	0.50	1.30	0.40	3.22	141	-0.03	0.21	-0.06	0.01	-0.03	-0.62	0.58
WEEK 68	140	1.39	0.50	1.31	0.50	3.28	140	-0.04	0.20	-0.07	-0.01	-0.05	-0.53	0.67
WEEK 72	171	1.40	0.51	1.32	0.52	3.05	171	-0.03	0.22	-0.07	0.00	-0.05	-0.63	0.67
WEEK 76	100	1.38	0.51	1.28	0.57	2.97	100	-0.01	0.20	-0.05	0.03	-0.02	-0.50	0.46

1. WEEK IS RELATIVE TO VISIT 1 OF STUDY 040
2. MAXIMUM OF THREE REPORTED VALUES OF FEV1 IS USED

TABLE 14.1B

DESCRIPTIVE STATISTICS FOR CHANGE FROM DAY 1 OF STUDY 040 IN FEV1 (L) BY WEEK - PATIENTS RANDOMIZED TO PLACEBO
IN STUDIES 042/091
PROTOCOL 040

WEEKLY ASSESSMENT							CHANGE FROM DAY 1							
WEEK	N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
WEEK 80	98	1.40	0.53	1.33	0.49	2.84	98	0.00	0.21	-0.04	0.05	0.01	-0.46	0.55
WEEK 84	162	1.41	0.52	1.33	0.50	3.19	162	-0.03	0.22	-0.06	0.01	-0.02	-0.51	0.57
WEEK 88	52	1.33	0.46	1.34	0.54	2.38	52	0.00	0.20	-0.06	0.06	-0.02	-0.54	0.57
WEEK 92	52	1.37	0.45	1.26	0.55	2.38	52	0.02	0.19	-0.03	0.07	0.02	-0.42	0.57
WEEK 96	158	1.40	0.51	1.34	0.49	3.18	158	-0.05	0.25	-0.08	-0.01	-0.06	-0.69	0.76
WEEK 100	21	1.34	0.37	1.33	0.61	2.19	21	0.06	0.20	-0.03	0.15	0.07	-0.31	0.52
WEEK 104	17	1.39	0.41	1.34	0.62	2.26	17	0.06	0.23	-0.06	0.17	0.05	-0.30	0.70
WEEK 108	129	1.40	0.54	1.32	0.52	3.36	129	-0.07	0.26	-0.12	-0.03	-0.09	-0.85	0.96
WEEK 112	9	1.45	0.40	1.32	0.93	2.17	9	0.00	0.13	-0.10	0.10	-0.03	-0.21	0.16
WEEK 116	9	1.49	0.39	1.31	1.08	2.21	9	0.04	0.16	-0.08	0.16	0.02	-0.19	0.35
WEEK 120	89	1.38	0.54	1.32	0.51	3.35	89	-0.09	0.25	-0.14	-0.04	-0.10	-0.73	0.69
WEEK 124	3	1.77	0.40	1.75	1.38	2.17	3	0.02	0.06	-0.13	0.17	0.01	-0.04	0.08
WEEK 128	3	1.64	0.56	1.69	1.06	2.18	3	-0.11	0.18	-0.55	0.34	-0.03	-0.31	0.02
WEEK 132	34	1.48	0.64	1.37	0.52	3.73	34	-0.12	0.35	-0.24	0.00	-0.16	-1.02	1.07
WEEK 136	1	1.73	.	1.73	1.73	1.73	1	0.06	.	.	.	0.06	0.06	0.06
ENDPOINT	232	1.36	0.49	1.28	0.51	3.73	232	-0.06	0.25	-0.09	-0.03	-0.07	-1.02	1.07

1. WEEK IS RELATIVE TO VISIT 1 OF STUDY 040
2. MAXIMUM OF THREE REPORTED VALUES OF FEV1 IS USED

TABLE 14.2A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN FVC (L) BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

WEEK	PRIOR TREATMENT	WEEKLY ASSESSMENT						CHANGE FROM BASELINE							
		N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
BASELINE	PLACEBO	232	2.81	0.75	2.75	1.41	5.49	.	.	.	.	.	.	.	.
	SB 207499	469	2.81	0.76	2.72	1.11	5.48	.	.	.	.	.	.	.	.
WEEK 2	PLACEBO	232	2.75	0.74	2.66	1.34	5.31	232	-0.06	0.35	-0.10	-0.01	-0.06	-1.25	1.21
	SB 207499	468	2.78	0.78	2.69	1.16	6.12	468	-0.03	0.34	-0.06	0.00	-0.01	-1.84	1.18
WEEK 4	PLACEBO	232	2.80	0.77	2.73	1.32	5.77	232	-0.02	0.35	-0.06	0.03	-0.02	-1.02	1.11
	SB 207499	468	2.78	0.77	2.69	1.15	6.57	468	-0.03	0.36	-0.06	0.01	0.00	-1.36	1.47
WEEK 8	PLACEBO	231	2.78	0.80	2.71	1.34	5.64	231	-0.03	0.34	-0.08	0.01	-0.01	-1.11	1.17
	SB 207499	469	2.82	0.78	2.68	1.18	5.71	469	0.02	0.36	-0.02	0.05	0.03	-1.47	1.30
WEEK 12	PLACEBO	230	2.77	0.73	2.70	1.35	5.34	230	-0.03	0.35	-0.08	0.01	-0.03	-1.18	0.91
	SB 207499	469	2.81	0.78	2.73	0.89	6.32	469	0.01	0.37	-0.02	0.04	0.02	-1.36	1.81
WEEK 16	PLACEBO	231	2.78	0.74	2.75	1.23	5.53	231	-0.03	0.39	-0.08	0.02	0.00	-1.76	1.09
	SB 207499	469	2.84	0.80	2.70	0.76	6.92	469	0.04	0.38	0.00	0.07	0.04	-1.89	1.58
WEEK 20	PLACEBO	232	2.77	0.75	2.69	1.31	5.83	232	-0.04	0.39	-0.09	0.01	-0.02	-1.41	1.54
	SB 207499	467	2.84	0.80	2.71	1.23	6.57	467	0.03	0.37	-0.00	0.06	0.04	-1.18	1.54
WEEK 24	PLACEBO	231	2.76	0.76	2.74	1.32	5.44	231	-0.05	0.38	-0.10	-0.00	-0.02	-1.11	1.12
	SB 207499	468	2.82	0.78	2.70	0.89	6.27	468	0.01	0.40	-0.03	0.05	0.02	-1.21	1.73
WEEK 26	PLACEBO	224	2.74	0.74	2.62	1.28	4.50	224	-0.06	0.37	-0.11	-0.01	-0.04	-1.20	1.15
	SB 207499	449	2.82	0.82	2.72	0.74	5.90	449	0.01	0.44	-0.03	0.05	0.01	-1.84	2.19
WEEK 28	PLACEBO	218	2.79	0.80	2.70	1.30	5.58	218	-0.02	0.43	-0.07	0.04	-0.01	-1.62	1.73
	SB 207499	456	2.79	0.79	2.66	1.17	6.07	456	-0.01	0.42	-0.05	0.02	0.00	-1.41	1.57
WEEK 32	PLACEBO	212	2.79	0.78	2.72	1.19	5.38	212	-0.01	0.41	-0.07	0.04	0.01	-1.38	1.23
	SB 207499	449	2.80	0.82	2.68	0.89	5.95	449	-0.02	0.43	-0.06	0.02	-0.02	-1.74	1.59
WEEK 36	PLACEBO	206	2.78	0.78	2.71	1.21	5.53	206	-0.02	0.42	-0.08	0.04	0.03	-1.56	1.54
	SB 207499	442	2.82	0.83	2.70	1.13	6.46	442	0.00	0.45	-0.04	0.04	0.02	-1.41	1.88
WEEK 40	PLACEBO	202	2.81	0.79	2.76	1.26	5.41	202	0.00	0.43	-0.06	0.06	0.00	-1.60	1.52
	SB 207499	434	2.85	0.82	2.74	0.88	6.22	434	0.02	0.42	-0.02	0.06	0.03	-1.11	2.09

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION
4. MAXIMUM OF THREE REPORTED VALUES OF FVC IS USED

TABLE 14.2A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN FVC (L) BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

WEEK	PRIOR TREATMENT	N	WEEKLY ASSESSMENT					N	CHANGE FROM BASELINE						
			MEAN	STD	MEDIAN	MIN	MAX		MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
WEEK 44	PLACEBO	196	2.78	0.77	2.75	1.06	5.05	196	-0.02	0.41	-0.08	0.04	0.03	-1.36	1.46
	SB 207499	433	2.81	0.80	2.74	0.99	5.18	433	-0.02	0.44	-0.06	0.03	0.00	-1.47	1.68
WEEK 48	PLACEBO	191	2.81	0.79	2.78	1.34	5.86	191	-0.00	0.42	-0.06	0.06	0.02	-1.70	1.60
	SB 207499	421	2.81	0.80	2.71	1.00	5.65	421	-0.02	0.42	-0.06	0.02	-0.03	-1.43	1.84
WEEK 52	PLACEBO	188	2.78	0.76	2.76	1.32	5.22	188	-0.04	0.44	-0.11	0.02	0.00	-1.88	1.63
	SB 207499	419	2.81	0.79	2.68	1.10	4.99	419	-0.01	0.43	-0.05	0.04	-0.01	-1.21	1.88
WEEK 56	PLACEBO	185	2.80	0.79	2.78	1.42	5.29	185	-0.01	0.42	-0.07	0.05	0.00	-1.52	1.27
	SB 207499	409	2.78	0.81	2.68	1.14	5.82	409	-0.03	0.44	-0.07	0.01	-0.03	-1.93	1.60
WEEK 60	PLACEBO	187	2.80	0.75	2.76	1.35	5.66	187	-0.00	0.44	-0.07	0.06	0.01	-1.89	1.52
	SB 207499	406	2.79	0.80	2.68	1.07	5.25	406	-0.02	0.44	-0.06	0.03	-0.02	-1.74	1.92
WEEK 64	PLACEBO	184	2.78	0.78	2.72	1.33	5.70	184	-0.02	0.46	-0.09	0.04	-0.01	-1.51	1.40
	SB 207499	402	2.76	0.79	2.66	0.91	5.19	402	-0.05	0.46	-0.09	-0.00	-0.04	-1.92	1.83
WEEK 68	PLACEBO	182	2.79	0.75	2.79	1.28	5.72	182	-0.02	0.45	-0.09	0.04	0.00	-1.88	1.56
	SB 207499	404	2.77	0.80	2.70	0.73	5.57	404	-0.03	0.44	-0.07	0.01	-0.04	-1.13	1.86
WEEK 72	PLACEBO	182	2.78	0.72	2.76	1.17	5.26	182	-0.04	0.45	-0.10	0.03	-0.02	-1.71	1.34
	SB 207499	397	2.76	0.79	2.67	0.90	4.78	397	-0.04	0.44	-0.08	0.00	-0.05	-1.36	1.79
WEEK 76	PLACEBO	180	2.78	0.77	2.78	1.24	5.26	180	-0.04	0.42	-0.10	0.03	0.00	-1.28	1.15
	SB 207499	381	2.74	0.77	2.65	0.99	4.55	381	-0.06	0.46	-0.10	-0.01	-0.04	-1.73	2.47
WEEK 80	PLACEBO	172	2.79	0.74	2.76	1.40	5.23	172	-0.04	0.46	-0.11	0.03	-0.01	-2.36	1.05
	SB 207499	363	2.75	0.78	2.63	0.56	5.30	363	-0.03	0.46	-0.08	0.01	0.00	-1.34	1.94
WEEK 84	PLACEBO	174	2.77	0.77	2.71	1.23	5.39	174	-0.03	0.48	-0.10	0.04	0.02	-1.84	1.25
	SB 207499	373	2.75	0.79	2.65	1.02	4.74	373	-0.05	0.46	-0.09	0.00	-0.02	-1.48	2.11
WEEK 88	PLACEBO	141	2.77	0.73	2.80	1.24	5.27	141	-0.04	0.45	-0.12	0.03	0.01	-1.61	1.68
	SB 207499	309	2.73	0.77	2.61	0.81	4.67	309	-0.03	0.46	-0.08	0.02	-0.02	-1.40	1.98
WEEK 92	PLACEBO	140	2.79	0.76	2.78	1.21	5.04	140	-0.04	0.45	-0.11	0.04	0.01	-2.03	1.09
	SB 207499	297	2.75	0.80	2.65	0.72	6.46	297	-0.02	0.50	-0.07	0.04	-0.02	-1.28	2.85

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION
4. MAXIMUM OF THREE REPORTED VALUES OF FVC IS USED

TABLE 14.2A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN FVC (L) BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

WEEK	PRIOR TREATMENT	N	WEEKLY ASSESSMENT					N	CHANGE FROM BASELINE						
			MEAN	STD	MEDIAN	MIN	MAX		MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
WEEK 96	PLACEBO	171	2.75	0.74	2.70	1.25	5.77	171	-0.07	0.48	-0.14	0.01	-0.03	-2.05	1.02
	SB 207499	357	2.74	0.78	2.63	1.18	5.03	357	-0.05	0.45	-0.10	-0.01	-0.06	-1.31	1.83
WEEK 100	PLACEBO	100	2.77	0.75	2.69	1.30	5.31	100	0.02	0.42	-0.07	0.10	0.04	-1.43	1.38
	SB 207499	198	2.69	0.76	2.59	1.25	4.78	198	-0.06	0.46	-0.12	0.01	-0.04	-1.42	1.16
WEEK 104	PLACEBO	98	2.77	0.80	2.81	1.31	5.44	98	0.01	0.50	-0.08	0.11	0.07	-1.84	1.39
	SB 207499	191	2.68	0.74	2.62	1.13	4.34	191	-0.06	0.44	-0.13	0.00	-0.02	-1.48	1.66
WEEK 108	PLACEBO	162	2.75	0.74	2.71	1.20	4.85	162	-0.06	0.45	-0.13	0.01	-0.04	-1.49	1.17
	SB 207499	333	2.72	0.79	2.65	0.88	5.03	333	-0.07	0.48	-0.12	-0.02	-0.08	-1.34	1.65
WEEK 112	PLACEBO	52	2.71	0.72	2.65	1.59	5.15	52	0.01	0.48	-0.13	0.14	0.07	-1.60	1.08
	SB 207499	95	2.62	0.68	2.61	1.14	4.25	95	-0.07	0.42	-0.16	0.01	-0.07	-1.13	1.21
WEEK 116	PLACEBO	52	2.73	0.72	2.65	1.43	5.13	52	0.00	0.47	-0.13	0.13	0.08	-1.29	1.23
	SB 207499	93	2.60	0.69	2.65	1.20	4.16	93	-0.09	0.43	-0.18	0.00	-0.07	-1.19	0.95
WEEK 120	PLACEBO	158	2.74	0.76	2.71	1.13	5.07	158	-0.08	0.49	-0.16	-0.00	-0.04	-1.98	1.05
	SB 207499	327	2.72	0.77	2.70	0.91	4.80	327	-0.06	0.45	-0.11	-0.01	-0.08	-1.45	2.09
WEEK 124	PLACEBO	21	2.68	0.54	2.68	1.68	3.84	21	0.01	0.33	-0.14	0.16	0.07	-0.65	0.57
	SB 207499	48	2.76	0.83	2.72	1.48	4.82	48	-0.06	0.43	-0.18	0.06	-0.02	-1.29	0.98
WEEK 128	PLACEBO	17	2.75	0.57	2.79	1.63	4.03	17	-0.03	0.32	-0.20	0.13	-0.02	-0.54	0.69
	SB 207499	40	2.67	0.82	2.59	1.34	4.26	40	-0.11	0.41	-0.24	0.02	0.01	-1.12	0.37
WEEK 132	PLACEBO	129	2.70	0.75	2.68	1.35	4.95	129	-0.14	0.50	-0.23	-0.05	-0.06	-2.17	1.36
	SB 207499	271	2.74	0.78	2.64	0.92	4.48	271	-0.06	0.48	-0.12	-0.00	-0.04	-1.48	2.06
WEEK 136	PLACEBO	9	2.59	0.67	2.44	1.84	3.95	9	-0.13	0.45	-0.48	0.22	-0.01	-1.05	0.37
	SB 207499	18	2.61	0.96	2.43	1.09	4.16	18	-0.05	0.47	-0.28	0.18	0.02	-1.37	0.74
WEEK 140	PLACEBO	9	2.71	0.62	2.81	1.85	3.83	9	-0.01	0.33	-0.26	0.24	0.07	-0.55	0.38
	SB 207499	16	2.46	0.80	2.29	1.62	4.15	16	-0.13	0.40	-0.35	0.08	-0.13	-0.83	0.52
WEEK 144	PLACEBO	89	2.68	0.75	2.64	1.40	4.90	89	-0.13	0.55	-0.24	-0.01	-0.02	-2.34	1.31
	SB 207499	187	2.68	0.81	2.58	0.87	4.71	187	-0.04	0.47	-0.11	0.02	-0.06	-1.24	2.12

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION
4. MAXIMUM OF THREE REPORTED VALUES OF FVC IS USED

TABLE 14.2A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN FVC (L) BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

		WEEKLY ASSESSMENT						CHANGE FROM BASELINE							
WEEK	PRIOR TREATMENT	N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
WEEK 148	PLACEBO SB 207499	3	3.08	0.94	3.11	2.12	4.00	3	0.15	0.17	-0.28	0.58	0.24	-0.05	0.26
		3	2.63	0.82	2.77	1.75	3.38	3	0.23	0.67	-1.44	1.90	0.06	-0.34	0.97
WEEK 152	PLACEBO SB 207499	3	2.88	1.00	2.86	1.89	3.88	3	-0.05	0.11	-0.31	0.21	-0.01	-0.17	0.03
		3	2.37	0.55	2.58	1.74	2.78	3	-0.04	0.26	-0.69	0.61	0.05	-0.33	0.17
WEEK 156	PLACEBO SB 207499	34	2.71	0.81	2.68	1.35	5.09	34	-0.22	0.64	-0.45	-0.00	-0.08	-1.74	1.50
		58	2.54	0.82	2.44	0.79	4.71	58	-0.10	0.57	-0.25	0.05	-0.12	-1.67	1.66
WEEK 160	PLACEBO SB 207499	1	3.02	.	3.02	3.02	3.02	1	0.15	.	.	.	0.15	0.15	0.15
		2	2.17	0.93	2.17	1.51	2.83	2	-0.23	0.07	-0.87	0.41	-0.23	-0.28	-0.18
ENDPOINT	PLACEBO SB 207499	232	2.68	0.73	2.64	1.13	5.09	232	-0.14	0.51	-0.20	-0.07	-0.06	-2.34	1.50
		469	2.75	0.79	2.66	0.79	5.57	469	-0.06	0.48	-0.10	-0.01	-0.04	-1.78	2.12

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION
4. MAXIMUM OF THREE REPORTED VALUES OF FVC IS USED

TABLE 14.2B

DESCRIPTIVE STATISTICS FOR CHANGE FROM DAY 1 OF STUDY 040 IN FVC (L) BY WEEK - PATIENTS RANDOMIZED TO PLACEBO
IN STUDIES 042/091
PROTOCOL 040

WEEKLY ASSESSMENT							CHANGE FROM DAY 1							
WEEK	N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
DAY 1	232	2.76	0.76	2.74	1.32	5.52	.	.	.	.	.	.	.	.
WEEK 2	224	2.74	0.74	2.62	1.28	4.50	224	-0.00	0.29	-0.04	0.04	0.01	-0.96	1.30
WEEK 4	218	2.79	0.80	2.70	1.30	5.58	218	0.04	0.32	-0.00	0.08	0.03	-1.31	1.76
WEEK 8	212	2.79	0.78	2.72	1.19	5.38	212	0.04	0.30	-0.00	0.08	0.04	-1.07	0.95
WEEK 12	206	2.78	0.78	2.71	1.21	5.53	206	0.03	0.33	-0.01	0.08	0.04	-1.25	0.97
WEEK 16	202	2.81	0.79	2.76	1.26	5.41	202	0.05	0.34	-0.00	0.09	0.06	-1.29	1.11
WEEK 20	196	2.78	0.77	2.75	1.06	5.05	196	0.02	0.33	-0.02	0.07	0.04	-1.10	1.00
WEEK 24	191	2.81	0.79	2.78	1.34	5.86	191	0.03	0.31	-0.01	0.08	0.04	-1.37	0.94
WEEK 28	188	2.78	0.76	2.76	1.32	5.22	188	-0.00	0.36	-0.06	0.05	0.02	-1.35	0.84
WEEK 32	185	2.80	0.79	2.78	1.42	5.29	185	0.03	0.34	-0.02	0.08	-0.01	-1.01	1.07
WEEK 36	187	2.80	0.75	2.76	1.35	5.66	187	0.03	0.36	-0.02	0.08	0.03	-1.01	1.00
WEEK 40	184	2.78	0.78	2.72	1.33	5.70	184	0.01	0.39	-0.05	0.07	0.01	-1.18	1.26
WEEK 44	182	2.79	0.75	2.79	1.28	5.72	182	0.01	0.36	-0.04	0.06	-0.02	-1.23	1.19
WEEK 48	182	2.78	0.72	2.76	1.17	5.26	182	-0.00	0.35	-0.05	0.05	0.00	-1.00	1.12
WEEK 52	180	2.78	0.77	2.78	1.24	5.26	180	-0.01	0.34	-0.06	0.04	0.01	-0.97	0.84
WEEK 56	172	2.79	0.74	2.76	1.40	5.23	172	-0.01	0.37	-0.06	0.05	-0.01	-1.24	1.01
WEEK 60	174	2.77	0.77	2.71	1.23	5.39	174	-0.00	0.41	-0.06	0.06	-0.01	-1.70	1.10
WEEK 64	141	2.77	0.73	2.80	1.24	5.27	141	-0.02	0.37	-0.09	0.04	-0.01	-1.09	1.14
WEEK 68	140	2.79	0.76	2.78	1.21	5.04	140	-0.03	0.37	-0.09	0.03	-0.07	-1.19	1.02
WEEK 72	171	2.75	0.74	2.70	1.25	5.77	171	-0.04	0.40	-0.10	0.02	-0.06	-1.89	0.98
WEEK 76	100	2.77	0.75	2.69	1.30	5.31	100	-0.01	0.40	-0.09	0.07	0.00	-1.37	1.41

1. WEEK IS RELATIVE TO VISIT 1 OF STUDY 040
2. MAXIMUM OF THREE REPORTED VALUES OF FVC IS USED

TABLE 14.2B

DESCRIPTIVE STATISTICS FOR CHANGE FROM DAY 1 OF STUDY 040 IN FVC (L) BY WEEK - PATIENTS RANDOMIZED TO PLACEBO
IN STUDIES 042/091
PROTOCOL 040

WEEKLY ASSESSMENT							CHANGE FROM DAY 1							
WEEK	N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
WEEK 80	98	2.77	0.80	2.81	1.31	5.44	98	-0.01	0.47	-0.11	0.08	-0.01	-2.38	1.24
WEEK 84	162	2.75	0.74	2.71	1.20	4.85	162	-0.03	0.37	-0.09	0.02	-0.04	-1.12	0.78
WEEK 88	52	2.71	0.72	2.65	1.59	5.15	52	-0.03	0.38	-0.14	0.08	0.03	-1.29	0.70
WEEK 92	52	2.73	0.72	2.65	1.43	5.13	52	-0.03	0.39	-0.14	0.08	-0.05	-1.16	1.01
WEEK 96	158	2.74	0.76	2.71	1.13	5.07	158	-0.05	0.42	-0.12	0.02	-0.08	-1.23	1.26
WEEK 100	21	2.68	0.54	2.68	1.68	3.84	21	-0.00	0.30	-0.14	0.14	-0.07	-0.42	0.65
WEEK 104	17	2.75	0.57	2.79	1.63	4.03	17	-0.02	0.31	-0.18	0.14	-0.08	-0.52	0.92
WEEK 108	129	2.70	0.75	2.68	1.35	4.95	129	-0.12	0.46	-0.20	-0.04	-0.12	-2.19	1.55
WEEK 112	9	2.59	0.67	2.44	1.84	3.95	9	-0.16	0.29	-0.38	0.06	-0.06	-0.76	0.12
WEEK 116	9	2.71	0.62	2.81	1.85	3.83	9	-0.04	0.21	-0.20	0.12	-0.07	-0.28	0.40
WEEK 120	89	2.68	0.75	2.64	1.40	4.90	89	-0.14	0.47	-0.24	-0.04	-0.12	-2.03	1.16
WEEK 124	3	3.08	0.94	3.11	2.12	4.00	3	0.04	0.17	-0.39	0.47	0.00	-0.11	0.23
WEEK 128	3	2.88	1.00	2.86	1.89	3.88	3	-0.16	0.12	-0.46	0.14	-0.23	-0.23	-0.02
WEEK 132	34	2.71	0.81	2.68	1.35	5.09	34	-0.29	0.55	-0.48	-0.09	-0.23	-2.16	0.55
WEEK 136	1	3.02	.	3.02	3.02	3.02	1	0.14	.	.	.	0.14	0.14	0.14
ENDPOINT	232	2.68	0.73	2.64	1.13	5.09	232	-0.08	0.47	-0.14	-0.02	-0.08	-2.19	1.18

1. WEEK IS RELATIVE TO VISIT 1 OF STUDY 040
2. MAXIMUM OF THREE REPORTED VALUES OF FVC IS USED

TABLE 14.3A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN PEFR (L/MIN) BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

WEEK	PRIOR TREATMENT	N	WEEKLY ASSESSMENT					N	CHANGE FROM BASELINE						
			MEAN	STD	MEDIAN	MIN	MAX		MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
BASELINE	PLACEBO	232	200.1	73.3	187.8	76.8	529.2	.	.	.	.	.	.	.	.
	SB 207499	469	204.7	74.8	196.2	51.0	597.6	.	.	.	.	.	.	.	.
WEEK 2	PLACEBO	232	200.0	71.9	196.2	60.0	460.8	232	-0.1	36.3	-4.8	4.6	0.0	-136.8	119.4
	SB 207499	468	205.8	74.9	196.2	68.4	546.0	468	1.0	38.0	-2.5	4.4	0.0	-136.8	273.0
WEEK 4	PLACEBO	232	200.7	73.6	187.8	68.4	503.4	232	0.6	34.5	-3.9	5.0	0.0	-85.8	136.8
	SB 207499	468	205.1	74.8	196.2	68.4	554.4	468	0.4	37.7	-3.0	3.8	0.0	-136.8	196.2
WEEK 8	PLACEBO	231	200.8	76.8	196.2	60.0	511.8	231	0.4	38.5	-4.5	5.4	0.0	-102.6	238.8
	SB 207499	469	207.0	76.5	196.2	60.0	537.6	469	2.3	38.4	-1.2	5.7	0.0	-111.0	204.6
WEEK 12	PLACEBO	230	201.2	75.4	196.2	60.0	486.6	230	1.0	35.7	-3.6	5.7	0.0	-85.8	179.4
	SB 207499	469	208.7	77.8	196.2	60.0	563.4	469	4.0	42.1	0.2	7.8	0.0	-111.0	222.0
WEEK 16	PLACEBO	230	202.1	76.7	196.2	68.4	503.4	230	1.6	39.7	-3.5	6.8	0.0	-136.8	247.2
	SB 207499	467	209.6	78.2	196.2	60.0	571.8	467	4.6	42.0	0.8	8.4	0.0	-136.8	264.6
WEEK 20	PLACEBO	232	199.6	77.2	187.8	76.8	503.4	232	-0.5	43.6	-6.2	5.1	0.0	-145.2	256.2
	SB 207499	467	208.7	77.0	196.2	51.0	597.6	467	3.7	42.1	-0.1	7.5	0.0	-162.6	221.4
WEEK 24	PLACEBO	231	199.3	75.6	187.8	68.4	495.0	231	-1.1	42.0	-6.6	4.3	0.0	-128.4	222.0
	SB 207499	468	206.7	77.7	196.2	68.4	563.4	468	1.9	47.2	-2.4	6.2	0.0	-119.4	307.2
WEEK 26	PLACEBO	224	201.5	78.1	187.8	76.8	511.8	224	2.5	41.4	-3.0	7.9	0.0	-94.2	247.2
	SB 207499	449	209.6	80.5	196.2	60.0	529.2	449	4.8	54.1	-0.2	9.8	0.0	-153.6	366.6
WEEK 28	PLACEBO	218	204.1	75.2	196.2	51.0	495.0	218	3.9	42.1	-1.7	9.5	0.0	-179.4	238.8
	SB 207499	455	208.6	79.8	196.2	42.6	563.4	455	4.2	55.5	-1.0	9.3	0.0	-170.4	341.4
WEEK 32	PLACEBO	212	204.8	78.7	196.2	68.4	511.8	212	5.0	43.4	-0.9	10.8	0.0	-136.8	256.2
	SB 207499	449	208.6	80.8	196.2	51.0	563.4	449	3.1	55.6	-2.1	8.2	0.0	-162.6	418.2
WEEK 36	PLACEBO	205	203.9	76.7	196.2	68.4	511.8	205	3.2	43.1	-2.8	9.1	0.0	-145.2	238.8
	SB 207499	442	209.0	80.3	196.2	34.2	546.0	442	3.1	52.9	-1.9	8.0	0.0	-179.4	349.8
WEEK 40	PLACEBO	202	206.0	74.8	196.2	68.4	495.0	202	5.9	41.2	0.2	11.6	0.0	-145.2	256.2
	SB 207499	434	212.6	82.4	196.2	60.0	563.4	434	7.0	55.7	1.8	12.3	0.0	-179.4	375.0

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION
4. MAXIMUM OF THREE REPORTED VALUES OF PEFR IS USED

TABLE 14.3A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN PEFR (L/MIN) BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

WEEK	PRIOR TREATMENT	N	WEEKLY ASSESSMENT					N	CHANGE FROM BASELINE						
			MEAN	STD	MEDIAN	MIN	MAX		MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
WEEK 44	PLACEBO	196	205.2	77.0	196.2	51.0	503.4	196	5.7	41.3	-0.1	11.5	0.0	-119.4	238.8
	SB 207499	433	209.5	80.0	196.2	51.0	580.2	433	4.1	54.5	-1.1	9.2	0.0	-136.8	426.6
WEEK 48	PLACEBO	191	204.9	80.1	196.2	68.4	511.8	191	3.6	43.6	-2.6	9.9	0.0	-111.0	264.6
	SB 207499	421	208.2	82.0	187.8	34.2	563.4	421	3.1	54.7	-2.2	8.3	-8.4	-196.2	289.8
WEEK 52	PLACEBO	188	204.4	76.3	196.2	68.4	486.6	188	3.1	44.6	-3.3	9.5	0.0	-153.6	256.2
	SB 207499	419	208.9	82.8	196.2	25.8	554.4	419	3.6	57.2	-1.9	9.1	0.0	-145.2	341.4
WEEK 56	PLACEBO	185	204.1	76.8	187.8	68.4	486.6	185	2.7	44.0	-3.7	9.1	0.0	-136.8	247.2
	SB 207499	409	207.1	81.6	196.2	34.2	554.4	409	2.4	55.7	-3.0	7.8	0.0	-171.0	358.2
WEEK 60	PLACEBO	187	204.6	74.2	196.2	76.8	469.2	187	3.2	45.0	-3.3	9.7	0.0	-187.8	238.8
	SB 207499	406	210.2	80.7	196.2	42.6	554.4	406	5.2	57.5	-0.4	10.8	0.0	-162.6	341.4
WEEK 64	PLACEBO	184	204.7	78.6	187.8	76.8	511.8	184	4.4	44.3	-2.1	10.8	0.0	-136.8	247.2
	SB 207499	402	208.0	80.3	196.2	42.6	503.4	402	3.3	57.7	-2.4	8.9	0.0	-153.6	375.0
WEEK 68	PLACEBO	182	204.0	74.7	196.2	76.8	460.8	182	2.7	41.5	-3.3	8.8	0.0	-119.4	213.6
	SB 207499	404	206.0	80.5	187.8	34.2	520.8	404	1.9	56.1	-3.5	7.4	-8.4	-171.0	307.2
WEEK 72	PLACEBO	182	202.2	75.4	192.1	76.8	486.6	182	0.6	45.7	-6.1	7.3	0.0	-162.6	238.8
	SB 207499	397	206.8	81.2	196.2	42.6	537.6	397	2.2	58.3	-3.6	7.9	-8.4	-136.8	392.4
WEEK 76	PLACEBO	180	203.0	78.9	192.0	60.0	477.6	180	0.4	45.3	-6.3	7.0	0.0	-128.4	238.8
	SB 207499	381	204.2	78.5	187.8	34.2	546.0	381	1.1	58.8	-4.9	7.0	-8.4	-196.2	341.4
WEEK 80	PLACEBO	172	204.7	78.0	187.8	68.4	460.8	172	1.3	47.1	-5.8	8.4	0.0	-145.2	204.6
	SB 207499	363	204.7	80.8	196.2	42.6	546.0	363	2.2	60.9	-4.1	8.5	-8.4	-171.0	375.0
WEEK 84	PLACEBO	174	206.0	77.2	196.2	68.4	469.2	174	4.5	45.7	-2.3	11.3	0.0	-153.6	238.8
	SB 207499	373	203.8	81.5	187.8	34.2	529.2	373	-1.0	54.9	-6.6	4.6	-8.4	-230.4	316.2
WEEK 88	PLACEBO	141	201.1	81.1	196.2	60.0	469.2	141	1.7	48.7	-6.4	9.9	0.0	-187.8	222.0
	SB 207499	309	204.4	80.5	187.8	34.2	554.4	309	2.5	59.1	-4.1	9.1	-8.4	-187.8	341.4
WEEK 92	PLACEBO	140	199.3	80.4	187.8	68.4	477.6	140	-1.6	44.2	-8.9	5.8	-8.4	-136.2	222.0
	SB 207499	297	204.3	82.6	187.8	34.2	640.2	297	1.5	64.1	-5.8	8.8	-8.4	-162.6	503.4

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION
4. MAXIMUM OF THREE REPORTED VALUES OF PEFR IS USED

TABLE 14.3A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN PEFR (L/MIN) BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

WEEK	PRIOR TREATMENT	N	WEEKLY ASSESSMENT					N	CHANGE FROM BASELINE						
			MEAN	STD	MEDIAN	MIN	MAX		MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
WEEK 96	PLACEBO	171	202.3	81.6	187.8	51.0	477.6	171	0.3	50.6	-7.3	8.0	0.0	-187.8	196.2
	SB 207499	357	204.8	80.6	196.2	42.6	563.4	357	-0.7	57.5	-6.7	5.3	-8.4	-238.8	307.2
WEEK 100	PLACEBO	100	198.1	81.6	187.8	42.6	486.6	100	3.3	46.2	-5.9	12.5	0.0	-110.4	171.0
	SB 207499	198	191.0	71.0	179.4	2.3	421.8	198	-6.4	53.8	-14.0	1.1	-8.4	-187.8	239.4
WEEK 104	PLACEBO	98	201.3	83.9	179.4	51.0	460.8	98	5.6	50.9	-4.7	15.8	4.2	-145.2	179.4
	SB 207499	191	194.6	73.5	187.8	76.8	460.8	191	-3.3	59.3	-11.8	5.2	-8.4	-179.4	307.2
WEEK 108	PLACEBO	162	201.9	77.9	187.8	68.4	460.8	162	0.2	50.6	-7.6	8.1	0.0	-171.0	222.0
	SB 207499	333	204.5	78.7	187.8	51.0	546.0	333	-0.7	55.2	-6.6	5.3	-8.4	-153.6	264.6
WEEK 112	PLACEBO	52	192.6	71.6	192.0	60.0	392.4	52	5.5	41.3	-6.0	17.0	0.0	-102.6	94.2
	SB 207499	95	192.5	68.7	187.8	76.8	361.0	95	-9.6	37.7	-17.3	-2.0	-9.0	-119.4	119.4
WEEK 116	PLACEBO	52	199.3	74.4	187.8	60.0	375.6	52	8.6	38.5	-2.1	19.3	8.7	-68.4	119.4
	SB 207499	93	193.1	68.7	187.8	68.4	392.4	93	-8.0	43.1	-16.8	0.9	-9.0	-128.4	136.8
WEEK 120	PLACEBO	158	205.5	81.1	196.2	51.0	469.2	158	2.3	51.7	-5.8	10.5	0.0	-187.8	222.0
	SB 207499	327	205.1	82.2	187.8	51.0	537.6	327	-0.4	58.1	-6.7	5.9	-8.4	-179.4	341.4
WEEK 124	PLACEBO	21	192.2	78.5	179.4	42.6	367.2	21	9.4	41.3	-9.4	28.2	9.0	-93.6	102.6
	SB 207499	48	197.6	80.1	174.9	76.8	435.0	48	8.2	70.1	-12.2	28.5	-8.4	-67.8	307.2
WEEK 128	PLACEBO	17	195.2	77.4	204.6	51.0	384.0	17	-0.5	33.8	-17.8	16.9	0.0	-42.6	76.8
	SB 207499	40	183.7	76.8	179.4	68.4	486.6	40	-7.4	69.9	-29.8	14.9	-12.6	-111.0	358.8
WEEK 132	PLACEBO	129	204.0	82.5	196.2	51.0	460.8	129	1.1	52.7	-8.1	10.2	-8.4	-127.8	213.6
	SB 207499	268	204.4	78.7	196.2	68.4	546.0	268	-2.3	56.6	-9.1	4.5	-8.4	-179.4	256.2
WEEK 136	PLACEBO	9	226.6	71.4	222.0	119.4	358.2	9	-2.7	48.4	-40.0	34.5	16.8	-85.2	51.0
	SB 207499	18	153.1	55.2	149.4	68.4	273.0	18	-6.7	33.2	-23.2	9.8	-4.2	-60.0	60.0
WEEK 140	PLACEBO	9	230.5	80.1	222.0	102.6	384.0	9	1.1	50.7	-37.9	40.1	17.4	-67.8	76.8
	SB 207499	16	146.1	44.3	141.0	68.4	222.0	16	-11.7	33.1	-29.3	5.9	-21.3	-60.0	42.6
WEEK 144	PLACEBO	89	202.4	87.4	187.8	42.6	486.6	89	-0.1	49.7	-10.6	10.3	-8.4	-128.4	162.6
	SB 207499	187	203.1	88.4	187.8	60.0	582.0	187	3.2	60.6	-5.5	12.0	-8.4	-187.8	282.0

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION
4. MAXIMUM OF THREE REPORTED VALUES OF PEFR IS USED

TABLE 14.3A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN PEFR (L/MIN) BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

		WEEKLY ASSESSMENT						CHANGE FROM BASELINE							
WEEK	PRIOR TREATMENT	N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
WEEK 148	PLACEBO SB 207499	3	284.4	87.2	247.2	222.0	384.0	3	51.2	30.5	-24.7	127.1	59.4	17.4	76.8
		3	165.0	34.3	145.2	145.2	204.6	3	11.4	24.9	-50.6	73.4	25.8	-17.4	25.8
WEEK 152	PLACEBO SB 207499	3	267.4	105.3	238.8	179.4	384.0	3	34.2	42.6	-71.6	140.0	34.2	-8.4	76.8
		3	147.8	34.6	127.8	127.8	187.8	3	-5.8	24.6	-66.9	55.3	8.4	-34.2	8.4
WEEK 156	PLACEBO SB 207499	34	204.8	85.2	192.0	85.2	418.2	34	-11.2	56.1	-30.8	8.3	-25.2	-136.2	153.6
		58	178.0	65.5	170.4	34.2	375.6	58	-6.8	56.9	-21.8	8.2	-17.4	-102.6	196.2
WEEK 160	PLACEBO SB 207499	1	238.8	.	238.8	238.8	238.8	1	34.2	.	.	.	34.2	34.2	34.2
		2	136.5	36.1	136.5	111.0	162.0	2	-34.2	36.5	-362.0	293.6	-34.2	-60.0	-8.4
ENDPOINT	PLACEBO SB 207499	232	195.4	74.3	187.8	42.6	486.6	232	-4.7	46.5	-10.7	1.3	-8.4	-153.6	213.6
		469	202.6	79.1	187.8	34.2	582.0	469	-2.1	56.3	-7.2	3.0	-8.4	-187.8	282.0

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION
4. MAXIMUM OF THREE REPORTED VALUES OF PEFR IS USED

TABLE 14.3B

DESCRIPTIVE STATISTICS FOR CHANGE FROM DAY 1 OF STUDY 040 IN PEFR (L/MIN) BY WEEK - PATIENTS RANDOMIZED TO PLACEBO
IN STUDIES 042/091
PROTOCOL 040

WEEKLY ASSESSMENT							CHANGE FROM DAY 1							
WEEK	N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
DAY 1	232	202.4	77.6	192.0	68.4	495.0	.	.	.	.	.	.	.	.
WEEK 2	224	201.5	78.1	187.8	76.8	511.8	224	1.8	29.8	-2.2	5.7	0.0	-128.4	102.6
WEEK 4	218	204.1	75.2	196.2	51.0	495.0	218	2.4	31.3	-1.7	6.6	0.0	-213.0	111.0
WEEK 8	212	204.8	78.7	196.2	68.4	511.8	212	2.9	28.2	-0.9	6.7	0.0	-67.8	136.8
WEEK 12	205	203.9	76.7	196.2	68.4	511.8	205	1.1	33.2	-3.5	5.7	0.0	-127.8	110.4
WEEK 16	202	206.0	74.8	196.2	68.4	495.0	202	2.8	31.7	-1.6	7.2	0.0	-111.0	120.0
WEEK 20	196	205.2	77.0	196.2	51.0	503.4	196	1.9	29.4	-2.2	6.1	0.0	-111.0	102.0
WEEK 24	191	204.9	80.1	196.2	68.4	511.8	191	-0.3	35.0	-5.3	4.7	0.0	-179.4	102.6
WEEK 28	188	204.4	76.3	196.2	68.4	486.6	188	-1.1	31.6	-5.7	3.4	0.0	-102.6	85.8
WEEK 32	185	204.1	76.8	187.8	68.4	486.6	185	-1.2	31.9	-5.8	3.5	0.0	-94.2	94.2
WEEK 36	187	204.6	74.2	196.2	76.8	469.2	187	-0.7	34.2	-5.7	4.2	0.0	-128.4	85.8
WEEK 40	184	204.7	78.6	187.8	76.8	511.8	184	0.0	35.4	-5.1	5.2	0.0	-145.2	111.0
WEEK 44	182	204.0	74.7	196.2	76.8	460.8	182	-1.8	31.6	-6.4	2.8	-4.2	-127.8	126.6
WEEK 48	182	202.2	75.4	192.1	76.8	486.6	182	-3.4	36.1	-8.7	1.9	0.0	-187.8	111.0
WEEK 52	180	203.0	78.9	192.0	60.0	477.6	180	-3.9	33.6	-8.8	1.1	0.0	-145.2	76.8
WEEK 56	172	204.7	78.0	187.8	68.4	460.8	172	-2.5	35.8	-7.9	2.9	-8.4	-111.0	128.4
WEEK 60	174	206.0	77.2	196.2	68.4	469.2	174	0.1	36.9	-5.4	5.6	-8.4	-102.6	119.4
WEEK 64	141	201.1	81.1	196.2	60.0	469.2	141	-4.3	35.3	-10.1	1.6	-8.4	-119.4	102.6
WEEK 68	140	199.3	80.4	187.8	68.4	477.6	140	-7.4	32.4	-12.8	-2.0	-8.4	-85.2	93.6
WEEK 72	171	202.3	81.6	187.8	51.0	477.6	171	-4.5	40.0	-10.5	1.6	-8.4	-136.8	127.8
WEEK 76	100	198.1	81.6	187.8	42.6	486.6	100	-1.0	34.5	-7.8	5.9	-8.4	-85.2	111.0

1. WEEK IS RELATIVE TO VISIT 1 OF STUDY 040
2. MAXIMUM OF THREE REPORTED VALUES OF PEFR IS USED

TABLE 14.3B

DESCRIPTIVE STATISTICS FOR CHANGE FROM DAY 1 OF STUDY 040 IN PEFR (L/MIN) BY WEEK - PATIENTS RANDOMIZED TO PLACEBO
IN STUDIES 042/091
PROTOCOL 040

WEEKLY ASSESSMENT							CHANGE FROM DAY 1							
WEEK	N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
WEEK 80	98	201.3	83.9	179.4	51.0	460.8	98	1.3	36.6	-6.0	8.6	-8.4	-76.8	145.2
WEEK 84	162	201.9	77.9	187.8	68.4	460.8	162	-4.8	38.6	-10.8	1.2	-8.4	-136.8	162.0
WEEK 88	52	192.6	71.6	192.0	60.0	392.4	52	-0.6	31.8	-9.4	8.3	-8.4	-59.4	85.2
WEEK 92	52	199.3	74.4	187.8	60.0	375.6	52	3.4	29.8	-4.9	11.7	0.0	-59.4	68.4
WEEK 96	158	205.5	81.1	196.2	51.0	469.2	158	-2.9	38.2	-8.9	3.1	-8.4	-94.2	119.4
WEEK 100	21	192.2	78.5	179.4	42.6	367.2	21	2.8	33.2	-12.3	18.0	8.4	-51.6	76.8
WEEK 104	17	195.2	77.4	204.6	51.0	384.0	17	-7.6	25.7	-20.8	5.7	0.0	-68.4	42.6
WEEK 108	129	204.0	82.5	196.2	51.0	460.8	129	-7.0	39.7	-13.9	-0.1	-8.4	-93.6	127.8
WEEK 112	9	226.6	71.4	222.0	119.4	358.2	9	-16.2	18.2	-30.2	-2.2	-17.4	-42.6	16.8
WEEK 116	9	230.5	80.1	222.0	102.6	384.0	9	-12.3	24.5	-31.2	6.5	0.0	-60.0	8.4
WEEK 120	89	202.4	87.4	187.8	42.6	486.6	89	-11.5	36.8	-19.2	-3.7	-16.8	-102.0	119.4
WEEK 124	3	284.4	87.2	247.2	222.0	384.0	3	8.4	22.2	-46.8	63.6	0.0	-8.4	33.6
WEEK 128	3	267.4	105.3	238.8	179.4	384.0	3	-8.6	22.6	-64.7	47.5	0.0	-34.2	8.4
WEEK 132	34	204.8	85.2	192.0	85.2	418.2	34	-21.2	43.7	-36.4	-5.9	-17.4	-119.4	119.4
WEEK 136	1	238.8	.	238.8	238.8	238.8	1	8.4	.	.	.	8.4	8.4	8.4
ENDPOINT	232	195.4	74.3	187.8	42.6	486.6	232	-7.0	37.9	-11.9	-2.1	-8.4	-119.4	119.4

1. WEEK IS RELATIVE TO VISIT 1 OF STUDY 040
2. MAXIMUM OF THREE REPORTED VALUES OF PEFR IS USED

TABLE 14.4A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN FEF25-75 (L/SEC) BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

WEEK	PRIOR TREATMENT	WEEKLY ASSESSMENT						CHANGE FROM BASELINE							
		N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
BASELINE	PLACEBO	232	0.67	0.34	0.61	0.17	2.32	.	.	.	.	.	.	.	.
	SB 207499	469	0.72	0.41	0.62	0.12	2.92	.	.	.	.	.	.	.	.
WEEK 2	PLACEBO	232	0.66	0.34	0.60	0.19	2.38	232	-0.02	0.17	-0.04	0.01	-0.01	-0.93	0.74
	SB 207499	468	0.73	0.43	0.63	0.15	3.32	468	0.01	0.22	-0.01	0.03	0.00	-0.87	2.06
WEEK 4	PLACEBO	232	0.67	0.36	0.61	0.17	2.55	232	-0.01	0.18	-0.03	0.02	-0.01	-0.90	1.05
	SB 207499	468	0.73	0.45	0.62	0.13	3.52	468	0.01	0.23	-0.01	0.03	0.01	-0.73	2.26
WEEK 8	PLACEBO	231	0.67	0.36	0.59	0.17	2.60	231	-0.01	0.18	-0.03	0.01	-0.01	-0.94	0.92
	SB 207499	469	0.72	0.43	0.61	0.13	3.41	469	0.00	0.23	-0.02	0.02	0.00	-0.77	2.15
WEEK 12	PLACEBO	230	0.65	0.35	0.58	0.16	2.18	230	-0.01	0.20	-0.04	0.01	-0.01	-0.95	1.24
	SB 207499	469	0.74	0.44	0.62	0.12	3.36	469	0.01	0.23	-0.01	0.04	0.00	-0.72	2.10
WEEK 16	PLACEBO	230	0.67	0.38	0.58	0.17	2.87	230	-0.01	0.21	-0.04	0.02	-0.02	-0.98	1.18
	SB 207499	467	0.74	0.46	0.61	0.19	3.93	467	0.02	0.26	-0.01	0.04	0.00	-0.81	2.67
WEEK 20	PLACEBO	232	0.65	0.39	0.56	0.14	2.93	232	-0.02	0.22	-0.05	0.01	-0.02	-0.97	1.00
	SB 207499	467	0.73	0.45	0.62	0.15	3.91	467	0.01	0.26	-0.01	0.03	0.00	-0.85	2.65
WEEK 24	PLACEBO	231	0.65	0.37	0.55	0.16	2.72	231	-0.02	0.21	-0.05	0.01	-0.02	-0.98	0.85
	SB 207499	467	0.73	0.45	0.61	0.16	4.18	467	0.01	0.27	-0.02	0.03	0.00	-0.90	2.92
WEEK 26	PLACEBO	224	0.66	0.38	0.57	0.17	2.89	224	-0.01	0.22	-0.04	0.02	-0.02	-0.93	0.85
	SB 207499	447	0.73	0.47	0.61	0.17	4.03	447	0.01	0.27	-0.02	0.03	-0.01	-0.76	2.77
WEEK 28	PLACEBO	218	0.67	0.40	0.59	0.18	3.00	218	-0.01	0.23	-0.04	0.02	-0.03	-1.05	1.03
	SB 207499	454	0.73	0.47	0.61	0.19	4.23	454	0.01	0.28	-0.01	0.04	-0.01	-0.68	2.97
WEEK 32	PLACEBO	212	0.67	0.39	0.62	0.17	2.71	212	-0.01	0.23	-0.04	0.03	-0.02	-1.07	1.22
	SB 207499	449	0.73	0.48	0.60	0.19	4.70	449	0.00	0.28	-0.02	0.03	-0.01	-0.91	3.44
WEEK 36	PLACEBO	206	0.67	0.39	0.59	0.16	2.94	206	-0.00	0.23	-0.03	0.03	-0.01	-0.90	1.10
	SB 207499	442	0.73	0.46	0.62	0.16	4.02	442	0.01	0.29	-0.02	0.03	-0.01	-0.93	2.76
WEEK 40	PLACEBO	201	0.66	0.37	0.60	0.18	2.53	201	-0.02	0.21	-0.05	0.01	0.01	-1.05	0.76
	SB 207499	434	0.73	0.47	0.61	0.13	4.10	434	0.00	0.27	-0.02	0.03	-0.02	-0.92	2.84

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION
4. MAXIMUM OF THREE REPORTED VALUES OF FEF25-75 IS USED

TABLE 14.4A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN FEF25-75 (L/SEC) BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

WEEK	PRIOR TREATMENT	N	WEEKLY ASSESSMENT					N	CHANGE FROM BASELINE						
			MEAN	STD	MEDIAN	MIN	MAX		MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
WEEK 44	PLACEBO	195	0.68	0.39	0.58	0.17	2.56	195	0.00	0.21	-0.03	0.03	0.00	-0.83	0.84
	SB 207499	432	0.72	0.46	0.62	0.19	4.34	432	-0.00	0.29	-0.03	0.03	-0.02	-1.29	3.08
WEEK 48	PLACEBO	189	0.66	0.41	0.56	0.19	3.00	189	-0.01	0.23	-0.05	0.02	-0.03	-0.89	1.13
	SB 207499	420	0.72	0.47	0.60	0.15	4.29	420	-0.01	0.28	-0.03	0.02	-0.02	-1.25	3.03
WEEK 52	PLACEBO	188	0.67	0.41	0.54	0.22	2.72	188	-0.01	0.25	-0.04	0.03	-0.01	-1.14	1.28
	SB 207499	417	0.72	0.49	0.59	0.18	4.81	417	-0.01	0.31	-0.03	0.02	-0.01	-0.94	3.55
WEEK 56	PLACEBO	183	0.67	0.39	0.57	0.18	2.82	183	-0.01	0.23	-0.05	0.02	-0.02	-0.98	0.96
	SB 207499	408	0.73	0.49	0.59	0.18	4.59	408	-0.00	0.30	-0.03	0.03	-0.02	-1.02	3.33
WEEK 60	PLACEBO	187	0.66	0.39	0.58	0.18	2.85	187	-0.02	0.24	-0.05	0.02	-0.02	-1.34	0.85
	SB 207499	404	0.72	0.47	0.60	0.17	4.09	404	-0.00	0.28	-0.03	0.02	-0.01	-1.06	2.83
WEEK 64	PLACEBO	183	0.65	0.38	0.54	0.21	2.79	183	-0.03	0.23	-0.06	0.00	-0.03	-0.88	0.91
	SB 207499	399	0.74	0.49	0.61	0.18	4.23	399	0.00	0.30	-0.03	0.03	-0.02	-1.10	2.97
WEEK 68	PLACEBO	180	0.63	0.33	0.55	0.17	2.15	180	-0.05	0.20	-0.08	-0.02	-0.04	-0.91	0.55
	SB 207499	403	0.72	0.48	0.59	0.17	4.07	403	-0.01	0.30	-0.04	0.02	-0.02	-0.89	2.81
WEEK 72	PLACEBO	182	0.65	0.40	0.53	0.18	2.62	182	-0.03	0.27	-0.07	0.01	-0.03	-1.16	1.06
	SB 207499	395	0.72	0.47	0.59	0.16	3.67	395	-0.02	0.30	-0.04	0.01	-0.02	-1.23	2.41
WEEK 76	PLACEBO	179	0.65	0.40	0.55	0.16	2.52	179	-0.03	0.25	-0.07	0.00	-0.04	-0.93	0.90
	SB 207499	380	0.71	0.46	0.59	0.17	3.17	380	-0.02	0.28	-0.04	0.01	-0.03	-0.98	2.01
WEEK 80	PLACEBO	172	0.65	0.38	0.55	0.17	2.23	172	-0.04	0.24	-0.07	-0.00	-0.05	-1.15	0.59
	SB 207499	363	0.70	0.46	0.59	0.14	3.89	363	-0.02	0.29	-0.05	0.01	-0.02	-1.19	2.63
WEEK 84	PLACEBO	174	0.64	0.36	0.56	0.11	2.41	174	-0.04	0.25	-0.08	-0.01	-0.05	-1.10	0.77
	SB 207499	373	0.72	0.48	0.57	0.18	3.72	373	-0.02	0.29	-0.05	0.01	-0.03	-1.11	2.46
WEEK 88	PLACEBO	141	0.63	0.40	0.53	0.12	2.61	141	-0.03	0.22	-0.07	0.01	-0.05	-0.62	0.95
	SB 207499	309	0.67	0.44	0.56	0.17	3.53	309	-0.03	0.27	-0.06	0.00	-0.04	-0.76	2.27
WEEK 92	PLACEBO	140	0.62	0.38	0.53	0.14	2.44	140	-0.03	0.21	-0.07	0.00	-0.05	-0.55	0.63
	SB 207499	297	0.70	0.56	0.57	0.14	6.46	297	-0.01	0.45	-0.06	0.05	-0.03	-0.81	5.97

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION
4. MAXIMUM OF THREE REPORTED VALUES OF FEF25-75 IS USED

TABLE 14.4A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN FEF25-75 (L/SEC) BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

WEEK	PRIOR TREATMENT	N	WEEKLY ASSESSMENT					N	CHANGE FROM BASELINE						
			MEAN	STD	MEDIAN	MIN	MAX		MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
WEEK 96	PLACEBO	170	0.64	0.40	0.53	0.15	2.76	170	-0.05	0.25	-0.09	-0.01	-0.07	-1.17	1.12
	SB 207499	356	0.71	0.46	0.57	0.17	3.56	356	-0.04	0.30	-0.07	-0.01	-0.04	-1.16	2.30
WEEK 100	PLACEBO	100	0.62	0.41	0.50	0.16	2.28	100	-0.01	0.23	-0.06	0.03	-0.04	-0.45	1.11
	SB 207499	197	0.62	0.36	0.52	0.16	2.32	197	-0.05	0.23	-0.08	-0.01	-0.02	-0.95	0.89
WEEK 104	PLACEBO	98	0.63	0.42	0.53	0.13	2.13	98	-0.01	0.25	-0.06	0.04	-0.02	-0.55	1.51
	SB 207499	190	0.61	0.36	0.53	0.18	2.75	190	-0.05	0.23	-0.08	-0.02	-0.04	-0.95	0.93
WEEK 108	PLACEBO	162	0.65	0.42	0.58	0.14	2.61	162	-0.04	0.27	-0.08	0.00	-0.05	-1.30	1.29
	SB 207499	333	0.70	0.46	0.57	0.18	2.99	333	-0.03	0.28	-0.07	-0.00	-0.03	-1.07	1.64
WEEK 112	PLACEBO	52	0.54	0.29	0.51	0.15	1.39	52	-0.04	0.23	-0.10	0.03	-0.01	-0.65	0.49
	SB 207499	95	0.57	0.32	0.49	0.14	2.06	95	-0.03	0.21	-0.08	0.01	-0.03	-0.51	0.98
WEEK 116	PLACEBO	52	0.57	0.29	0.53	0.15	1.41	52	-0.02	0.19	-0.07	0.03	0.00	-0.51	0.51
	SB 207499	93	0.58	0.35	0.49	0.16	1.85	93	-0.02	0.23	-0.07	0.03	-0.05	-0.68	0.68
WEEK 120	PLACEBO	158	0.64	0.41	0.55	0.12	2.69	158	-0.05	0.30	-0.10	-0.00	-0.06	-1.28	1.21
	SB 207499	327	0.70	0.47	0.57	0.14	3.36	327	-0.04	0.29	-0.07	-0.01	-0.04	-1.01	2.10
WEEK 124	PLACEBO	21	0.58	0.28	0.60	0.14	1.03	21	0.06	0.23	-0.05	0.16	0.01	-0.54	0.60
	SB 207499	48	0.75	0.60	0.56	0.17	2.99	48	0.05	0.34	-0.05	0.15	0.01	-0.32	1.73
WEEK 128	PLACEBO	17	0.59	0.27	0.65	0.17	1.13	17	0.05	0.23	-0.07	0.17	0.01	-0.39	0.70
	SB 207499	40	0.71	0.60	0.51	0.24	3.64	40	0.05	0.34	-0.05	0.16	0.01	-0.30	1.82
WEEK 132	PLACEBO	128	0.64	0.39	0.55	0.17	2.20	128	-0.05	0.26	-0.10	-0.01	-0.07	-1.01	0.78
	SB 207499	267	0.71	0.47	0.56	0.15	3.13	267	-0.03	0.28	-0.07	0.00	-0.02	-0.82	1.61
WEEK 136	PLACEBO	9	0.68	0.22	0.72	0.35	0.92	9	0.06	0.19	-0.08	0.20	0.09	-0.23	0.38
	SB 207499	18	0.50	0.25	0.47	0.14	1.30	18	-0.07	0.15	-0.14	0.01	-0.07	-0.31	0.37
WEEK 140	PLACEBO	9	0.66	0.26	0.75	0.32	1.01	9	0.04	0.18	-0.10	0.18	0.06	-0.31	0.30
	SB 207499	16	0.51	0.26	0.44	0.22	1.17	16	-0.01	0.16	-0.09	0.08	-0.04	-0.34	0.34
WEEK 144	PLACEBO	89	0.63	0.43	0.54	0.13	2.61	89	-0.05	0.28	-0.11	0.01	-0.06	-0.96	1.17
	SB 207499	187	0.69	0.49	0.54	0.17	3.38	187	-0.03	0.31	-0.07	0.02	-0.05	-0.97	2.12

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION
4. MAXIMUM OF THREE REPORTED VALUES OF FEF25-75 IS USED

TABLE 14.4A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN FEF25-75 (L/SEC) BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

		WEEKLY ASSESSMENT						CHANGE FROM BASELINE							
WEEK	PRIOR TREATMENT	N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
WEEK 148	PLACEBO SB 207499	3	0.75	0.08	0.75	0.67	0.82	3	0.00	0.29	-0.71	0.72	0.04	-0.30	0.27
		3	0.51	0.20	0.41	0.39	0.74	3	-0.06	0.10	-0.31	0.19	-0.11	-0.12	0.06
WEEK 152	PLACEBO SB 207499	3	0.72	0.19	0.77	0.51	0.88	3	-0.02	0.20	-0.51	0.46	0.03	-0.24	0.14
		3	0.48	0.14	0.45	0.35	0.63	3	-0.09	0.17	-0.52	0.33	-0.16	-0.22	0.10
WEEK 156	PLACEBO SB 207499	34	0.76	0.58	0.69	0.17	2.95	34	-0.03	0.34	-0.15	0.09	-0.05	-0.84	1.31
		58	0.60	0.34	0.51	0.18	1.91	58	-0.09	0.23	-0.15	-0.02	-0.10	-0.94	0.70
WEEK 160	PLACEBO SB 207499	1	0.85	.	0.85	0.85	0.85	1	-0.27	.	.	.	-0.27	-0.27	-0.27
		2	0.44	0.20	0.44	0.30	0.58	2	-0.24	0.04	-0.62	0.14	-0.24	-0.27	-0.21
ENDPOINT	PLACEBO SB 207499	232	0.62	0.38	0.52	0.13	2.95	232	-0.05	0.26	-0.09	-0.02	-0.04	-1.28	1.31
		469	0.67	0.43	0.56	0.14	3.38	469	-0.05	0.28	-0.07	-0.02	-0.05	-1.47	2.12

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION
4. MAXIMUM OF THREE REPORTED VALUES OF FEF25-75 IS USED

TABLE 14.5A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN FEF75 (L/SEC) BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

WEEK	PRIOR TREATMENT	WEEKLY ASSESSMENT						CHANGE FROM BASELINE							
		N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
BASELINE	PLACEBO	232	0.32	0.21	0.29	0.05	2.05	.	.	.	.	.	.	.	.
	SB 207499	469	0.35	0.30	0.28	0.09	4.03	.	.	.	.	.	.	.	.
WEEK 2	PLACEBO	232	0.32	0.22	0.28	0.08	2.02	232	-0.00	0.16	-0.03	0.02	-0.01	-0.89	1.39
	SB 207499	468	0.33	0.23	0.27	0.06	1.94	468	-0.02	0.23	-0.04	0.00	-0.01	-3.71	1.13
WEEK 4	PLACEBO	232	0.32	0.21	0.27	0.07	2.02	232	-0.01	0.12	-0.02	0.01	0.00	-0.91	0.53
	SB 207499	468	0.34	0.24	0.27	0.08	1.74	468	-0.02	0.23	-0.04	0.00	0.00	-3.84	0.68
WEEK 8	PLACEBO	231	0.31	0.18	0.26	0.09	1.19	231	-0.02	0.15	-0.04	0.00	-0.01	-1.08	0.66
	SB 207499	469	0.33	0.22	0.26	0.07	1.67	469	-0.02	0.22	-0.04	-0.00	-0.01	-3.62	0.57
WEEK 12	PLACEBO	230	0.30	0.18	0.26	0.04	1.23	230	-0.01	0.13	-0.03	0.00	-0.01	-0.97	0.46
	SB 207499	467	0.34	0.24	0.27	0.05	2.06	467	-0.02	0.24	-0.04	0.01	-0.01	-3.82	1.73
WEEK 16	PLACEBO	230	0.30	0.20	0.25	0.07	2.08	230	-0.02	0.15	-0.04	-0.00	-0.01	-0.92	0.80
	SB 207499	467	0.33	0.22	0.27	0.07	1.57	467	-0.02	0.23	-0.04	0.00	-0.01	-3.69	0.94
WEEK 20	PLACEBO	232	0.32	0.27	0.26	0.07	2.99	232	-0.01	0.25	-0.04	0.03	-0.01	-0.95	2.71
	SB 207499	466	0.33	0.22	0.28	0.05	1.73	466	-0.02	0.24	-0.05	-0.00	-0.01	-3.77	0.78
WEEK 24	PLACEBO	231	0.30	0.17	0.26	0.06	1.22	231	-0.02	0.14	-0.04	-0.01	-0.01	-1.02	0.47
	SB 207499	468	0.34	0.31	0.27	0.07	5.00	468	-0.02	0.31	-0.04	0.01	-0.01	-3.72	3.93
WEEK 26	PLACEBO	224	0.30	0.18	0.26	0.05	1.07	224	-0.02	0.16	-0.04	0.00	-0.02	-0.98	0.60
	SB 207499	447	0.33	0.24	0.27	0.05	1.83	447	-0.02	0.25	-0.04	0.00	-0.01	-3.80	0.90
WEEK 28	PLACEBO	218	0.31	0.21	0.26	0.08	1.89	218	-0.02	0.16	-0.04	0.00	-0.02	-0.90	0.82
	SB 207499	454	0.33	0.23	0.27	0.04	2.27	454	-0.02	0.25	-0.04	0.01	-0.01	-3.79	1.76
WEEK 32	PLACEBO	211	0.31	0.21	0.28	0.08	2.05	211	-0.01	0.17	-0.04	0.01	-0.01	-1.03	0.77
	SB 207499	449	0.33	0.23	0.26	0.05	1.93	449	-0.02	0.24	-0.04	0.00	-0.01	-3.74	0.98
WEEK 36	PLACEBO	205	0.30	0.19	0.26	0.07	1.53	205	-0.02	0.15	-0.04	0.00	-0.01	-1.00	0.48
	SB 207499	442	0.33	0.21	0.27	0.07	1.48	442	-0.03	0.24	-0.05	-0.00	-0.01	-3.74	0.96
WEEK 40	PLACEBO	199	0.30	0.18	0.27	0.07	1.56	199	-0.02	0.16	-0.05	-0.00	-0.01	-1.20	0.42
	SB 207499	434	0.33	0.21	0.28	0.04	1.65	434	-0.03	0.23	-0.05	-0.00	0.00	-3.65	0.70

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION
4. MAXIMUM OF THREE REPORTED VALUES OF FEF75 IS USED

TABLE 14.5A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN FEF75 (L/SEC) BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

WEEK	PRIOR TREATMENT	N	WEEKLY ASSESSMENT					N	CHANGE FROM BASELINE						
			MEAN	STD	MEDIAN	MIN	MAX		MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
WEEK 44	PLACEBO	194	0.31	0.18	0.26	0.05	1.17	194	-0.02	0.15	-0.04	0.00	-0.02	-1.08	0.37
	SB 207499	432	0.33	0.21	0.27	0.07	1.89	432	-0.03	0.22	-0.05	-0.01	-0.01	-3.26	0.94
WEEK 48	PLACEBO	189	0.30	0.22	0.25	0.05	2.03	189	-0.02	0.17	-0.05	0.00	-0.02	-0.87	0.75
	SB 207499	420	0.33	0.22	0.27	0.07	1.87	420	-0.03	0.24	-0.05	-0.01	-0.01	-3.77	0.90
WEEK 52	PLACEBO	188	0.31	0.22	0.26	0.06	2.06	188	-0.02	0.19	-0.04	0.01	-0.01	-1.10	0.78
	SB 207499	417	0.33	0.24	0.26	0.05	2.04	417	-0.03	0.24	-0.05	-0.00	-0.01	-3.67	1.09
WEEK 56	PLACEBO	183	0.30	0.17	0.26	0.08	1.10	183	-0.03	0.16	-0.05	-0.01	-0.02	-0.95	0.63
	SB 207499	408	0.34	0.24	0.27	0.07	1.99	408	-0.02	0.25	-0.05	0.00	-0.01	-3.74	0.96
WEEK 60	PLACEBO	187	0.30	0.20	0.25	0.09	1.53	187	-0.02	0.16	-0.05	-0.00	-0.02	-0.89	0.42
	SB 207499	404	0.34	0.30	0.26	0.06	3.52	404	-0.02	0.30	-0.05	0.01	-0.01	-3.77	2.64
WEEK 64	PLACEBO	184	0.30	0.19	0.24	0.03	1.15	184	-0.03	0.17	-0.06	-0.01	-0.03	-0.92	0.79
	SB 207499	400	0.33	0.24	0.28	0.04	2.40	400	-0.02	0.27	-0.05	0.00	-0.00	-3.74	1.96
WEEK 68	PLACEBO	180	0.29	0.15	0.25	0.07	1.21	180	-0.04	0.16	-0.06	-0.02	-0.03	-1.31	0.22
	SB 207499	403	0.32	0.22	0.27	0.07	1.64	403	-0.03	0.26	-0.06	-0.01	-0.01	-3.78	0.75
WEEK 72	PLACEBO	180	0.30	0.21	0.25	0.07	1.83	180	-0.03	0.18	-0.06	-0.00	-0.02	-1.18	0.56
	SB 207499	397	0.32	0.21	0.26	0.04	1.42	397	-0.04	0.25	-0.06	-0.01	-0.01	-3.75	0.79
WEEK 76	PLACEBO	178	0.29	0.19	0.24	0.06	1.63	178	-0.04	0.17	-0.06	-0.01	-0.03	-1.19	0.49
	SB 207499	380	0.32	0.23	0.26	0.06	2.13	380	-0.04	0.26	-0.06	-0.01	-0.01	-3.82	1.36
WEEK 80	PLACEBO	172	0.30	0.20	0.25	0.07	1.68	172	-0.03	0.18	-0.06	-0.00	-0.03	-1.07	0.47
	SB 207499	362	0.32	0.22	0.26	0.06	1.59	362	-0.03	0.26	-0.06	-0.01	-0.01	-3.84	0.82
WEEK 84	PLACEBO	174	0.29	0.17	0.25	0.05	1.37	174	-0.04	0.20	-0.07	-0.01	-0.03	-1.72	0.44
	SB 207499	373	0.33	0.24	0.26	0.06	1.81	373	-0.03	0.27	-0.06	-0.01	-0.02	-3.72	1.48
WEEK 88	PLACEBO	141	0.28	0.19	0.24	0.07	1.24	141	-0.04	0.16	-0.06	-0.01	-0.03	-1.10	0.79
	SB 207499	309	0.30	0.21	0.25	0.05	1.52	309	-0.04	0.27	-0.07	-0.01	-0.02	-3.73	0.76
WEEK 92	PLACEBO	140	0.27	0.17	0.23	0.07	0.98	140	-0.04	0.16	-0.07	-0.01	-0.02	-1.23	0.57
	SB 207499	297	0.32	0.26	0.25	0.06	2.91	297	-0.03	0.31	-0.07	0.00	-0.02	-3.74	2.60

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION
4. MAXIMUM OF THREE REPORTED VALUES OF FEF75 IS USED

TABLE 14.5A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN FEF75 (L/SEC) BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

WEEK	PRIOR TREATMENT	N	WEEKLY ASSESSMENT					N	CHANGE FROM BASELINE						
			MEAN	STD	MEDIAN	MIN	MAX		MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
WEEK 96	PLACEBO	171	0.31	0.31	0.23	0.08	3.62	171	-0.02	0.25	-0.06	0.01	-0.03	-1.13	2.34
	SB 207499	356	0.32	0.23	0.26	0.06	1.85	356	-0.04	0.28	-0.07	-0.01	-0.02	-3.81	0.95
WEEK 100	PLACEBO	100	0.28	0.20	0.23	0.05	1.65	100	-0.02	0.11	-0.04	0.00	-0.02	-0.33	0.37
	SB 207499	197	0.28	0.18	0.23	0.07	1.66	197	-0.04	0.17	-0.06	-0.01	-0.01	-1.43	0.39
WEEK 104	PLACEBO	97	0.27	0.21	0.23	0.03	1.31	97	-0.02	0.13	-0.05	0.00	-0.02	-0.33	0.60
	SB 207499	189	0.26	0.14	0.22	0.05	1.00	189	-0.05	0.17	-0.07	-0.03	-0.02	-1.38	0.27
WEEK 108	PLACEBO	161	0.30	0.20	0.24	0.08	1.55	161	-0.03	0.18	-0.06	-0.00	-0.02	-1.17	0.48
	SB 207499	331	0.32	0.23	0.25	0.07	1.68	331	-0.04	0.27	-0.07	-0.01	-0.02	-3.70	1.13
WEEK 112	PLACEBO	51	0.24	0.16	0.20	0.07	0.95	51	-0.03	0.14	-0.07	0.01	-0.03	-0.38	0.56
	SB 207499	93	0.25	0.13	0.22	0.09	0.89	93	-0.02	0.11	-0.04	0.01	-0.01	-0.39	0.48
WEEK 116	PLACEBO	51	0.24	0.11	0.23	0.09	0.56	51	-0.04	0.10	-0.07	-0.01	-0.03	-0.30	0.20
	SB 207499	91	0.25	0.14	0.23	0.07	0.69	91	-0.01	0.12	-0.04	0.01	-0.02	-0.38	0.46
WEEK 120	PLACEBO	157	0.30	0.26	0.24	0.01	2.45	157	-0.03	0.27	-0.07	0.02	-0.02	-1.38	2.23
	SB 207499	325	0.32	0.25	0.26	0.07	2.34	325	-0.04	0.20	-0.06	-0.02	-0.02	-1.69	0.92
WEEK 124	PLACEBO	20	0.26	0.11	0.28	0.06	0.44	20	-0.00	0.13	-0.06	0.06	-0.01	-0.39	0.24
	SB 207499	46	0.35	0.33	0.24	0.09	1.89	46	0.01	0.20	-0.05	0.07	-0.00	-0.53	0.94
WEEK 128	PLACEBO	17	0.26	0.13	0.24	0.09	0.51	17	-0.01	0.12	-0.07	0.06	-0.01	-0.22	0.29
	SB 207499	40	0.32	0.25	0.25	0.10	1.54	40	0.01	0.09	-0.02	0.04	0.00	-0.19	0.24
WEEK 132	PLACEBO	129	0.32	0.31	0.25	0.04	2.94	129	-0.02	0.27	-0.06	0.03	-0.03	-1.49	1.57
	SB 207499	267	0.33	0.25	0.26	0.05	1.96	267	-0.02	0.18	-0.04	0.00	-0.02	-0.77	1.08
WEEK 136	PLACEBO	9	0.27	0.09	0.29	0.15	0.41	9	-0.02	0.13	-0.12	0.08	-0.11	-0.16	0.23
	SB 207499	18	0.21	0.12	0.18	0.07	0.59	18	-0.05	0.06	-0.08	-0.01	-0.04	-0.16	0.12
WEEK 140	PLACEBO	9	0.28	0.11	0.29	0.13	0.40	9	-0.02	0.13	-0.12	0.08	-0.03	-0.15	0.22
	SB 207499	16	0.22	0.11	0.19	0.08	0.53	16	-0.02	0.07	-0.05	0.02	-0.03	-0.14	0.16
WEEK 144	PLACEBO	88	0.28	0.18	0.24	0.05	1.16	88	-0.04	0.15	-0.07	-0.01	-0.05	-0.86	0.41
	SB 207499	185	0.31	0.25	0.24	0.05	1.92	185	-0.02	0.18	-0.05	0.00	-0.01	-0.85	0.97

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION
4. MAXIMUM OF THREE REPORTED VALUES OF FEF75 IS USED

TABLE 14.5A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN FEF75 (L/SEC) BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

		WEEKLY ASSESSMENT						CHANGE FROM BASELINE							
WEEK	PRIOR TREATMENT	N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
WEEK 148	PLACEBO SB 207499	3	0.29	0.08	0.30	0.21	0.36	3	-0.07	0.10	-0.33	0.19	-0.04	-0.19	0.01
		3	0.21	0.05	0.19	0.18	0.27	3	-0.00	0.04	-0.09	0.08	0.00	-0.04	0.03
WEEK 152	PLACEBO SB 207499	3	0.29	0.08	0.29	0.22	0.37	3	-0.07	0.14	-0.42	0.28	-0.12	-0.18	0.09
		3	0.26	0.03	0.26	0.24	0.29	3	0.05	0.06	-0.10	0.19	0.07	-0.02	0.09
WEEK 156	PLACEBO SB 207499	34	0.39	0.45	0.29	0.07	2.68	34	-0.00	0.28	-0.10	0.10	-0.03	-0.35	1.40
		58	0.29	0.22	0.23	0.08	1.28	58	-0.04	0.14	-0.08	-0.01	-0.03	-0.53	0.45
WEEK 160	PLACEBO SB 207499	1	0.37	.	0.37	0.37	0.37	1	-0.12	.	.	.	-0.12	-0.12	-0.12
		2	0.20	0.06	0.20	0.16	0.24	2	-0.03	0.06	-0.54	0.48	-0.03	-0.07	0.01
ENDPOINT	PLACEBO SB 207499	232	0.30	0.28	0.24	0.05	2.94	232	-0.02	0.22	-0.05	0.01	-0.02	-1.49	1.57
		469	0.32	0.24	0.26	0.05	2.34	469	-0.04	0.20	-0.06	-0.02	-0.02	-1.69	0.97

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION
4. MAXIMUM OF THREE REPORTED VALUES OF FEF75 IS USED

SB 207499

TABLE 14.6A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN FEV6 (L) BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

WEEK	PRIOR TREATMENT	WEEKLY ASSESSMENT						CHANGE FROM BASELINE							
		N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
BASELINE	PLACEBO	163	2.59	0.66	2.54	1.27	4.65	.	.	.	.	.	.	.	.
	SB 207499	311	2.55	0.65	2.47	1.02	4.79	.	.	.	.	.	.	.	.
WEEK 2	PLACEBO	149	2.54	0.65	2.46	1.23	4.52	149	-0.05	0.28	-0.10	-0.01	-0.06	-1.01	0.97
	SB 207499	280	2.52	0.65	2.39	1.15	4.50	280	-0.02	0.25	-0.05	0.01	0.00	-1.11	0.77
WEEK 4	PLACEBO	147	2.55	0.64	2.53	1.19	4.48	147	-0.02	0.28	-0.06	0.03	0.00	-0.77	0.96
	SB 207499	276	2.49	0.63	2.43	1.21	4.48	276	-0.03	0.29	-0.07	0.00	-0.01	-1.30	0.98
WEEK 8	PLACEBO	145	2.56	0.69	2.52	1.16	4.57	145	-0.03	0.28	-0.07	0.02	-0.01	-0.85	0.73
	SB 207499	282	2.55	0.66	2.47	1.15	4.90	282	-0.00	0.26	-0.03	0.03	0.00	-1.13	0.63
WEEK 12	PLACEBO	139	2.48	0.62	2.45	1.20	4.22	139	-0.07	0.31	-0.12	-0.02	-0.07	-1.13	0.62
	SB 207499	286	2.53	0.67	2.45	0.86	5.13	286	-0.00	0.29	-0.04	0.03	0.02	-1.14	0.96
WEEK 16	PLACEBO	141	2.53	0.64	2.51	1.14	4.07	141	-0.04	0.30	-0.09	0.01	-0.03	-1.06	0.70
	SB 207499	275	2.54	0.66	2.43	0.75	4.68	275	0.02	0.27	-0.01	0.05	0.03	-0.79	0.80
WEEK 20	PLACEBO	143	2.50	0.68	2.46	1.14	4.98	143	-0.07	0.33	-0.12	-0.02	-0.07	-0.98	1.45
	SB 207499	282	2.56	0.67	2.48	1.17	4.73	282	0.03	0.30	-0.01	0.06	0.05	-0.82	0.86
WEEK 24	PLACEBO	147	2.52	0.65	2.47	1.24	4.19	147	-0.07	0.29	-0.12	-0.02	-0.02	-0.90	0.61
	SB 207499	283	2.53	0.64	2.45	0.87	4.75	283	0.02	0.31	-0.02	0.05	0.01	-0.93	1.59
WEEK 26	PLACEBO	141	2.51	0.65	2.46	1.26	4.02	141	-0.05	0.30	-0.10	-0.00	-0.02	-1.06	0.89
	SB 207499	264	2.53	0.67	2.49	1.18	4.54	264	-0.01	0.35	-0.05	0.03	-0.00	-1.09	1.35
WEEK 28	PLACEBO	131	2.57	0.65	2.53	1.23	4.38	131	-0.00	0.33	-0.06	0.05	0.00	-1.20	0.80
	SB 207499	272	2.52	0.67	2.44	1.16	4.60	272	-0.00	0.32	-0.04	0.04	0.02	-1.05	0.95
WEEK 32	PLACEBO	130	2.57	0.69	2.50	1.14	4.28	130	-0.01	0.32	-0.07	0.04	0.02	-1.18	0.62
	SB 207499	266	2.52	0.68	2.48	1.12	4.38	266	-0.01	0.32	-0.05	0.02	0.00	-1.27	0.96
WEEK 36	PLACEBO	126	2.57	0.66	2.56	1.18	4.16	126	0.01	0.32	-0.05	0.06	0.00	-1.13	0.92
	SB 207499	263	2.57	0.67	2.48	1.18	4.47	263	0.01	0.34	-0.03	0.05	0.00	-0.92	1.12
WEEK 40	PLACEBO	124	2.60	0.70	2.53	1.22	5.11	124	0.02	0.35	-0.04	0.09	0.00	-1.24	1.58
	SB 207499	260	2.57	0.68	2.50	1.11	4.41	260	0.01	0.33	-0.03	0.05	0.00	-0.81	1.14

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION
4. MAXIMUM OF THREE REPORTED VALUES OF FEV6 IS USED

SB 207499

TABLE 14.6A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN FEV6 (L) BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

WEEK	PRIOR TREATMENT	N	WEEKLY ASSESSMENT					N	CHANGE FROM BASELINE						
			MEAN	STD	MEDIAN	MIN	MAX		MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
WEEK 44	PLACEBO	118	2.58	0.67	2.53	1.21	5.01	118	-0.00	0.37	-0.07	0.07	0.03	-1.30	1.48
	SB 207499	260	2.55	0.69	2.49	0.94	4.27	260	-0.01	0.32	-0.05	0.03	0.00	-0.88	0.90
WEEK 48	PLACEBO	117	2.51	0.65	2.49	1.29	4.44	117	-0.04	0.32	-0.10	0.01	-0.02	-0.96	0.86
	SB 207499	243	2.55	0.70	2.43	1.17	4.68	243	-0.03	0.30	-0.07	0.01	-0.02	-1.01	0.90
WEEK 52	PLACEBO	114	2.56	0.69	2.50	1.27	5.20	114	-0.05	0.36	-0.11	0.02	-0.04	-1.13	1.67
	SB 207499	243	2.51	0.67	2.43	1.18	4.47	243	-0.02	0.30	-0.06	0.01	-0.03	-0.78	1.05
WEEK 56	PLACEBO	112	2.57	0.66	2.49	1.33	4.38	112	-0.02	0.34	-0.08	0.04	-0.01	-1.03	0.78
	SB 207499	235	2.53	0.68	2.46	1.04	4.96	235	-0.02	0.31	-0.06	0.02	-0.02	-1.01	0.85
WEEK 60	PLACEBO	113	2.56	0.66	2.50	1.29	5.10	113	-0.04	0.38	-0.11	0.03	-0.03	-1.10	1.57
	SB 207499	227	2.52	0.67	2.43	1.20	4.12	227	-0.01	0.32	-0.05	0.03	0.00	-1.05	0.80
WEEK 64	PLACEBO	112	2.52	0.68	2.42	1.28	4.80	112	-0.05	0.38	-0.13	0.02	-0.04	-1.02	1.27
	SB 207499	231	2.50	0.66	2.47	0.88	4.37	231	-0.04	0.35	-0.08	0.01	-0.01	-1.44	1.09
WEEK 68	PLACEBO	112	2.56	0.64	2.50	1.26	5.11	112	-0.04	0.37	-0.11	0.03	-0.04	-1.22	1.58
	SB 207499	229	2.50	0.66	2.47	1.33	4.26	229	-0.03	0.33	-0.08	0.01	-0.02	-0.96	0.98
WEEK 72	PLACEBO	110	2.49	0.62	2.40	1.15	4.11	110	-0.10	0.36	-0.16	-0.03	-0.07	-1.12	0.74
	SB 207499	224	2.49	0.67	2.44	0.92	4.41	224	-0.04	0.31	-0.08	0.00	-0.04	-0.77	0.77
WEEK 76	PLACEBO	105	2.52	0.64	2.45	1.10	3.99	105	-0.10	0.33	-0.16	-0.04	-0.06	-0.95	0.62
	SB 207499	217	2.48	0.61	2.43	1.22	4.11	217	-0.05	0.34	-0.09	-0.00	-0.05	-0.92	1.47
WEEK 80	PLACEBO	102	2.49	0.62	2.41	1.20	4.05	102	-0.10	0.33	-0.17	-0.03	-0.09	-1.11	0.95
	SB 207499	207	2.48	0.62	2.45	1.11	4.34	207	-0.02	0.32	-0.07	0.02	0.00	-0.78	1.02
WEEK 84	PLACEBO	104	2.52	0.70	2.45	1.05	4.81	104	-0.06	0.39	-0.13	0.02	-0.04	-1.30	1.28
	SB 207499	206	2.48	0.66	2.46	0.99	4.33	206	-0.04	0.34	-0.08	0.01	-0.03	-1.06	0.88
WEEK 88	PLACEBO	89	2.47	0.69	2.37	1.03	5.23	89	-0.11	0.40	-0.19	-0.02	-0.11	-1.47	1.70
	SB 207499	181	2.44	0.63	2.37	1.19	4.06	181	-0.03	0.31	-0.08	0.01	-0.05	-0.75	0.95
WEEK 92	PLACEBO	93	2.47	0.64	2.38	1.16	3.98	93	-0.12	0.36	-0.19	-0.04	-0.07	-1.14	0.75
	SB 207499	175	2.46	0.62	2.41	1.16	4.16	175	-0.02	0.32	-0.07	0.03	0.00	-1.21	0.89

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION
4. MAXIMUM OF THREE REPORTED VALUES OF FEV6 IS USED

SB 207499

TABLE 14.6A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN FEV6 (L) BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

WEEK	PRIOR TREATMENT	N	WEEKLY ASSESSMENT					N	CHANGE FROM BASELINE						
			MEAN	STD	MEDIAN	MIN	MAX		MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
WEEK 96	PLACEBO	98	2.47	0.64	2.37	1.24	4.32	98	-0.11	0.40	-0.19	-0.03	-0.11	-1.13	0.98
	SB 207499	198	2.47	0.62	2.42	1.18	4.00	198	-0.05	0.31	-0.10	-0.01	-0.05	-0.78	0.76
WEEK 100	PLACEBO	68	2.49	0.71	2.37	1.39	4.54	68	-0.01	0.37	-0.10	0.08	-0.02	-1.07	1.01
	SB 207499	123	2.40	0.61	2.36	1.32	4.27	123	-0.08	0.32	-0.13	-0.02	-0.10	-0.72	0.67
WEEK 104	PLACEBO	66	2.49	0.77	2.44	1.19	4.96	66	-0.05	0.46	-0.16	0.06	-0.03	-1.23	1.43
	SB 207499	118	2.40	0.58	2.41	1.33	3.78	118	-0.08	0.31	-0.14	-0.03	-0.07	-1.17	0.59
WEEK 108	PLACEBO	93	2.49	0.62	2.46	1.03	4.03	93	-0.12	0.39	-0.20	-0.04	-0.05	-1.19	0.75
	SB 207499	195	2.48	0.62	2.42	1.20	4.12	195	-0.06	0.33	-0.10	-0.01	-0.06	-0.84	0.98
WEEK 112	PLACEBO	36	2.33	0.68	2.26	1.23	3.77	36	-0.10	0.49	-0.26	0.06	-0.01	-1.31	0.91
	SB 207499	64	2.34	0.54	2.42	1.24	3.61	64	-0.10	0.32	-0.18	-0.02	-0.10	-0.73	0.68
WEEK 116	PLACEBO	37	2.44	0.66	2.39	1.28	3.95	37	-0.06	0.43	-0.20	0.08	0.00	-1.15	0.85
	SB 207499	63	2.29	0.56	2.33	1.12	3.55	63	-0.12	0.37	-0.21	-0.02	-0.08	-0.80	0.83
WEEK 120	PLACEBO	94	2.47	0.66	2.44	1.13	4.11	94	-0.13	0.41	-0.22	-0.05	-0.07	-1.34	0.84
	SB 207499	184	2.44	0.63	2.43	1.01	4.13	184	-0.08	0.34	-0.13	-0.03	-0.07	-0.89	0.98
WEEK 124	PLACEBO	13	2.37	0.44	2.34	1.60	3.45	13	-0.09	0.28	-0.26	0.07	-0.01	-0.56	0.27
	SB 207499	29	2.41	0.66	2.46	1.42	3.63	29	-0.05	0.30	-0.16	0.07	-0.05	-0.55	0.56
WEEK 128	PLACEBO	10	2.30	0.54	2.18	1.55	3.45	10	-0.21	0.26	-0.40	-0.02	-0.16	-0.68	0.08
	SB 207499	28	2.33	0.65	2.36	1.33	3.62	28	-0.11	0.34	-0.24	0.02	-0.11	-0.78	0.43
WEEK 132	PLACEBO	84	2.49	0.71	2.33	1.21	4.93	84	-0.17	0.47	-0.27	-0.07	-0.13	-1.43	1.40
	SB 207499	155	2.48	0.64	2.42	0.95	3.86	155	-0.08	0.35	-0.14	-0.03	-0.06	-1.02	0.88
WEEK 136	PLACEBO	4	2.41	0.64	2.12	2.03	3.36	4	-0.28	0.56	-1.16	0.61	-0.19	-1.02	0.29
	SB 207499	13	2.23	0.76	2.03	1.08	3.51	13	-0.14	0.29	-0.32	0.03	-0.04	-0.89	0.19
WEEK 140	PLACEBO	4	2.47	0.71	2.18	2.01	3.52	4	-0.21	0.49	-0.99	0.57	-0.09	-0.87	0.21
	SB 207499	13	2.22	0.73	1.85	1.41	3.50	13	-0.16	0.26	-0.32	-0.00	-0.16	-0.56	0.51
WEEK 144	PLACEBO	55	2.46	0.66	2.36	1.27	4.04	55	-0.19	0.43	-0.31	-0.08	-0.13	-1.26	0.98
	SB 207499	112	2.35	0.63	2.30	1.20	3.84	112	-0.09	0.30	-0.14	-0.03	-0.10	-0.83	0.77

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION
4. MAXIMUM OF THREE REPORTED VALUES OF FEV6 IS USED

TABLE 14.6A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN FEV6 (L) BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

		WEEKLY ASSESSMENT						CHANGE FROM BASELINE							
WEEK	PRIOR TREATMENT	N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
WEEK 148	PLACEBO	1	3.43	.	3.43	3.43	3.43	1	0.02	.	.	.	0.02	0.02	0.02
	SB 207499	3	2.34	0.59	2.64	1.66	2.72	3	0.09	0.48	-1.10	1.28	-0.01	-0.33	0.61
WEEK 152	PLACEBO	1	3.48	.	3.48	3.48	3.48	1	0.07	.	.	.	0.07	0.07	0.07
	SB 207499	3	2.22	0.53	2.40	1.63	2.64	3	-0.03	0.31	-0.80	0.74	-0.04	-0.33	0.29
WEEK 156	PLACEBO	21	2.59	0.84	2.37	1.13	5.08	21	-0.26	0.65	-0.55	0.04	-0.20	-1.80	1.55
	SB 207499	35	2.34	0.60	2.26	1.50	3.99	35	-0.06	0.39	-0.20	0.07	-0.13	-0.79	1.01
WEEK 160	SB 207499	2	2.04	0.84	2.04	1.44	2.63	2	-0.29	0.08	-0.98	0.41	-0.29	-0.34	-0.23
ENDPOINT	PLACEBO	163	2.46	0.68	2.37	1.13	5.08	163	-0.14	0.45	-0.21	-0.07	-0.10	-1.80	1.55
	SB 207499	311	2.48	0.67	2.44	1.01	4.96	311	-0.07	0.34	-0.11	-0.03	-0.05	-0.97	1.01

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION
4. MAXIMUM OF THREE REPORTED VALUES OF FEV6 IS USED

TABLE 14.7A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN TOTAL SCORE OF THE SGRQ BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

WEEK	PRIOR TREATMENT	WEEKLY ASSESSMENT						CHANGE FROM BASELINE							
		N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
BASELINE	PLACEBO	212	42.5	16.6	43.2	4.7	85.0	.	.	.	.	.	.	.	.
	SB 207499	453	42.3	17.7	42.1	0.9	90.5	.	.	.	.	.	.	.	.
WEEK 12	PLACEBO	207	37.0	17.0	35.4	1.8	86.9	207	-5.8	12.4	-7.5	-4.1	-4.2	-51.2	49.6
	SB 207499	437	36.9	18.0	35.2	0.9	88.2	437	-5.3	11.5	-6.4	-4.2	-4.5	-48.7	38.4
WEEK 24	PLACEBO	211	36.4	18.0	34.6	0.7	87.6	211	-6.1	13.2	-7.9	-4.3	-5.2	-46.4	29.6
	SB 207499	441	36.6	19.5	34.5	0.0	98.0	441	-5.7	12.0	-6.8	-4.5	-5.2	-57.2	25.8
WEEK 36	PLACEBO	195	33.5	16.6	32.5	1.8	81.1	195	-8.8	12.9	-10.6	-7.0	-6.8	-52.8	24.3
	SB 207499	406	35.4	20.4	32.1	0.0	98.8	406	-6.7	14.1	-8.1	-5.3	-6.6	-48.3	40.6
WEEK 48	PLACEBO	184	35.1	18.4	32.7	0.0	89.3	184	-8.1	15.5	-10.4	-5.9	-7.4	-49.0	54.8
	SB 207499	401	35.1	19.4	33.6	0.0	99.6	401	-6.7	13.8	-8.1	-5.4	-6.3	-48.7	33.2
WEEK 72	PLACEBO	170	35.7	17.5	33.1	0.0	90.2	170	-7.9	14.9	-10.2	-5.7	-6.6	-56.7	31.9
	SB 207499	379	34.3	20.1	30.3	0.0	93.9	379	-7.5	15.1	-9.0	-5.9	-7.3	-47.0	47.3
WEEK 96	PLACEBO	156	36.1	17.8	35.4	3.4	85.9	156	-7.2	15.3	-9.6	-4.8	-6.4	-55.0	39.7
	SB 207499	323	34.4	20.6	30.1	0.0	99.6	323	-7.1	15.2	-8.7	-5.4	-6.6	-47.8	50.2
WEEK 120	PLACEBO	144	34.1	18.2	31.3	0.0	85.7	144	-9.0	14.7	-11.4	-6.6	-6.3	-56.4	24.5
	SB 207499	290	35.1	20.7	31.7	0.0	93.6	290	-6.7	15.6	-8.5	-4.9	-5.7	-51.3	58.8
WEEK 144	PLACEBO	69	35.7	18.5	31.5	3.4	80.4	69	-6.6	16.7	-10.6	-2.6	-4.0	-54.3	33.6
	SB 207499	139	33.9	18.4	31.6	0.0	79.7	139	-6.8	15.8	-9.5	-4.2	-6.2	-45.7	59.7
ENDPOINT	PLACEBO	212	36.1	18.4	32.2	0.0	88.8	212	-6.4	14.9	-8.4	-4.4	-4.3	-54.3	33.6
	SB 207499	453	35.9	20.9	32.6	0.0	99.6	453	-6.4	16.1	-7.9	-4.9	-5.4	-51.3	59.7

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION

TABLE 14.7B

DESCRIPTIVE STATISTICS FOR CHANGE FROM DAY 1 OF STUDY 040 IN TOTAL SCORE OF THE SGRQ BY WEEK - PATIENTS RANDOMIZED TO PLACEBO
IN STUDIES 042/091
PROTOCOL 040

WEEKLY ASSESSMENT							CHANGE FROM DAY 1							
WEEK	N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
DAY 1	212	36.4	18.0	34.5	0.7	87.6	.	.	.	.	.	.	.	.
WEEK 12	196	33.5	16.6	32.1	1.8	81.1	196	-2.8	10.6	-4.3	-1.3	-1.7	-38.3	39.6
WEEK 24	184	35.0	18.5	32.3	0.0	89.3	184	-1.9	12.3	-3.7	-0.1	-2.5	-51.7	42.5
WEEK 48	170	35.6	17.4	33.1	0.0	90.2	170	-1.2	12.5	-3.1	0.7	-1.6	-41.9	41.0
WEEK 72	155	36.0	17.8	34.8	3.4	85.9	155	-0.6	13.7	-2.8	1.6	0.2	-46.1	64.1
WEEK 96	143	34.2	18.2	31.5	0.0	85.7	143	-2.1	14.1	-4.5	0.2	-1.5	-67.2	52.1
WEEK 120	69	35.7	18.5	31.5	3.4	80.4	69	2.1	13.3	-1.1	5.3	1.0	-22.1	55.1
ENDPOINT	212	36.2	18.4	32.3	0.0	88.8	212	-0.2	13.2	-2.0	1.6	0.4	-67.2	55.1

1. WEEK IS RELATIVE TO VISIT 1 OF STUDY 040

TABLE 14.8A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN SYMPTOMS SCORE OF THE SGRQ BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

WEEK	PRIOR TREATMENT	WEEKLY ASSESSMENT						CHANGE FROM BASELINE							
		N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
BASELINE	PLACEBO	214	53.0	21.3	51.9	7.5	100.0	.	.	.	.	.	.	.	.
	SB 207499	457	51.9	22.6	52.2	0.0	100.0	.	.	.	.	.	.	.	.
WEEK 12	PLACEBO	212	43.5	22.0	43.6	0.0	100.0	212	-9.5	21.8	-12.5	-6.5	-7.6	-65.6	52.9
	SB 207499	452	42.2	23.9	39.4	0.0	100.0	452	-9.7	19.8	-11.5	-7.8	-9.1	-64.7	43.9
WEEK 24	PLACEBO	213	41.9	23.1	39.4	0.0	95.3	213	-11.0	22.6	-14.0	-7.9	-7.9	-74.2	45.4
	SB 207499	451	41.5	24.5	38.8	0.0	100.0	451	-10.3	20.0	-12.1	-8.4	-9.7	-77.0	51.6
WEEK 36	PLACEBO	201	36.9	21.2	37.1	0.0	97.6	201	-16.0	21.5	-19.0	-13.1	-14.9	-81.3	35.5
	SB 207499	417	38.1	24.6	33.3	0.0	100.0	417	-13.9	22.4	-16.1	-11.8	-13.2	-92.8	57.8
WEEK 48	PLACEBO	188	38.9	24.1	37.1	0.0	93.9	188	-15.2	25.1	-18.8	-11.6	-17.7	-85.8	57.6
	SB 207499	417	37.6	24.4	33.5	0.0	100.0	417	-13.7	22.4	-15.9	-11.5	-12.8	-90.5	58.3
WEEK 72	PLACEBO	176	37.1	22.2	34.2	0.0	97.5	176	-16.8	23.4	-20.3	-13.3	-13.4	-76.9	37.7
	SB 207499	391	36.1	24.8	32.0	0.0	100.0	391	-15.5	22.8	-17.7	-13.2	-13.9	-86.8	55.3
WEEK 96	PLACEBO	159	39.3	23.2	38.6	0.0	100.0	159	-13.7	25.4	-17.7	-9.8	-15.7	-76.9	82.3
	SB 207499	333	37.1	25.3	33.9	0.0	100.0	333	-13.5	24.1	-16.1	-10.9	-13.3	-92.8	50.4
WEEK 120	PLACEBO	148	32.8	23.3	25.6	0.0	92.6	148	-19.5	23.0	-23.2	-15.8	-18.0	-83.6	40.9
	SB 207499	304	35.8	24.6	31.4	0.0	95.2	304	-14.5	25.2	-17.3	-11.6	-14.0	-90.5	58.9
WEEK 144	PLACEBO	71	37.2	21.7	37.4	0.0	100.0	71	-15.6	22.4	-20.9	-10.3	-16.2	-59.6	29.2
	SB 207499	144	34.6	23.4	33.1	0.0	95.3	144	-14.6	23.6	-18.5	-10.7	-16.9	-65.3	60.9
ENDPOINT	PLACEBO	214	38.2	23.2	35.0	0.0	100.0	214	-14.8	23.1	-17.9	-11.7	-14.3	-83.6	44.2
	SB 207499	457	38.0	24.7	35.6	0.0	100.0	457	-14.0	23.6	-16.1	-11.8	-13.6	-92.8	60.9

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION

TABLE 14.8B

DESCRIPTIVE STATISTICS FOR CHANGE FROM DAY 1 OF STUDY 040 IN SYMPTOMS SCORE OF THE SGRQ BY WEEK - PATIENTS RANDOMIZED TO PLACEBO
IN STUDIES 042/091
PROTOCOL 040

WEEKLY ASSESSMENT							CHANGE FROM DAY 1							
WEEK	N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
DAY 1	213	41.9	23.1	39.4	0.0	95.3	.	.	.	.	.	.	.	.
WEEK 12	200	36.9	21.3	37.0	0.0	97.6	200	-5.2	19.1	-7.8	-2.5	-3.6	-67.7	56.4
WEEK 24	187	38.9	24.2	36.8	0.0	93.9	187	-4.3	22.2	-7.5	-1.1	-3.0	-77.3	58.5
WEEK 48	175	37.1	22.2	33.7	0.0	97.5	175	-5.4	21.5	-8.6	-2.2	-6.3	-77.3	67.4
WEEK 72	158	39.2	23.2	38.5	0.0	100.0	158	-4.6	24.8	-8.5	-0.7	-5.7	-77.3	92.3
WEEK 96	147	32.7	23.4	25.4	0.0	92.6	147	-9.1	21.6	-12.6	-5.6	-9.3	-92.5	52.4
WEEK 120	71	37.2	21.7	37.4	0.0	100.0	71	-0.6	21.5	-5.7	4.5	0.5	-58.9	58.4
ENDPOINT	213	38.2	23.2	35.2	0.0	100.0	213	-3.7	21.7	-6.6	-0.8	-2.0	-92.5	58.4

1. WEEK IS RELATIVE TO VISIT 1 OF STUDY 040

TABLE 14.9A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN IMPACTS SCORE OF THE SGRQ BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

		WEEKLY ASSESSMENT						CHANGE FROM BASELINE							
		N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
BASELINE	PLACEBO	212	31.8	18.0	30.7	0.0	77.7	.	.	.	.	.	.	.	.
	SB 207499	453	31.5	19.2	30.0	0.0	92.1	.	.	.	.	.	.	.	.
WEEK 12	PLACEBO	207	26.6	17.9	22.6	0.0	81.7	207	-5.5	13.4	-7.4	-3.7	-3.7	-48.5	57.5
	SB 207499	437	26.8	18.2	24.0	0.0	92.8	437	-4.6	13.6	-5.9	-3.4	-3.6	-54.5	48.6
WEEK 24	PLACEBO	211	26.7	18.6	22.8	0.0	85.0	211	-5.1	14.5	-7.1	-3.1	-4.4	-44.9	41.6
	SB 207499	441	26.7	20.4	23.2	0.0	99.4	441	-4.8	14.1	-6.1	-3.5	-4.2	-57.0	52.2
WEEK 36	PLACEBO	195	24.1	17.1	21.0	0.0	79.3	195	-7.5	14.6	-9.6	-5.4	-6.3	-53.4	28.7
	SB 207499	407	26.1	21.3	22.1	0.0	100.0	407	-5.2	16.0	-6.8	-3.6	-4.7	-55.1	46.2
WEEK 48	PLACEBO	184	25.1	18.9	21.5	0.0	87.4	184	-7.4	16.9	-9.9	-5.0	-7.6	-50.2	69.3
	SB 207499	401	25.9	20.1	22.3	0.0	100.0	401	-5.1	15.8	-6.7	-3.6	-4.0	-59.1	46.2
WEEK 72	PLACEBO	171	26.5	18.4	22.7	0.0	87.4	171	-6.7	17.2	-9.3	-4.1	-4.8	-52.2	50.0
	SB 207499	379	25.0	20.3	19.8	0.0	93.3	379	-6.1	16.6	-7.8	-4.4	-5.8	-57.0	54.8
WEEK 96	PLACEBO	156	27.2	18.8	24.8	0.0	80.7	156	-5.6	16.7	-8.2	-2.9	-3.6	-51.4	33.2
	SB 207499	323	24.9	21.3	16.8	0.0	100.0	323	-6.2	17.0	-8.0	-4.3	-5.1	-62.3	69.3
WEEK 120	PLACEBO	144	25.3	18.7	20.4	0.0	78.0	144	-7.4	15.4	-10.0	-4.9	-4.4	-56.8	25.9
	SB 207499	290	26.5	21.0	20.7	0.0	95.9	290	-4.9	16.9	-6.8	-2.9	-3.6	-54.4	62.8
WEEK 144	PLACEBO	69	27.2	20.3	20.7	0.0	76.0	69	-5.2	18.3	-9.5	-0.8	-3.2	-48.6	37.0
	SB 207499	139	24.9	18.6	20.8	0.0	77.2	139	-5.2	18.1	-8.2	-2.1	-5.4	-58.9	73.3
ENDPOINT	PLACEBO	212	26.9	19.5	22.3	0.0	87.4	212	-4.9	16.3	-7.1	-2.7	-3.0	-48.6	37.0
	SB 207499	453	26.6	21.5	22.3	0.0	100.0	453	-4.8	17.8	-6.5	-3.2	-4.0	-59.1	73.3

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION

TABLE 14.9B

DESCRIPTIVE STATISTICS FOR CHANGE FROM DAY 1 OF STUDY 040 IN IMPACTS SCORE OF THE SGRQ BY WEEK - PATIENTS RANDOMIZED TO PLACEBO
IN STUDIES 042/091
PROTOCOL 040

WEEKLY ASSESSMENT							CHANGE FROM DAY 1							
WEEK	N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
DAY 1	212	26.7	18.6	22.8	0.0	85.0	.	.	.	.	.	.	.	.
WEEK 12	196	24.1	17.0	21.5	0.0	79.3	196	-2.5	12.7	-4.3	-0.8	-1.7	-44.8	33.5
WEEK 24	184	25.0	18.9	21.5	0.0	87.4	184	-2.0	13.2	-4.0	-0.1	-1.4	-68.9	38.7
WEEK 48	171	26.6	18.4	22.7	0.0	87.4	171	-0.4	14.4	-2.6	1.7	-1.4	-55.2	44.1
WEEK 72	155	27.3	18.8	24.9	0.0	80.7	155	1.0	14.9	-1.3	3.4	1.1	-55.3	59.7
WEEK 96	143	25.3	18.8	20.5	0.0	78.0	143	-1.1	14.7	-3.6	1.3	-0.9	-68.6	45.7
WEEK 120	69	27.2	20.3	20.7	0.0	76.0	69	2.4	14.3	-1.0	5.9	0.5	-25.6	54.5
ENDPOINT	212	27.0	19.5	22.4	0.0	87.4	212	0.4	14.4	-1.6	2.3	0.0	-68.6	54.5

1. WEEK IS RELATIVE TO VISIT 1 OF STUDY 040

TABLE 14.10A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN ACTIVITIES SCORE OF THE SGRQ BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

		WEEKLY ASSESSMENT						CHANGE FROM BASELINE							
		N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
BASELINE	PLACEBO	212	55.4	19.9	54.6	0.0	93.4	.	.	.	.	.	.	.	.
	SB 207499	453	55.6	21.0	59.5	0.0	100.0	.	.	.	.	.	.	.	.
WEEK 12	PLACEBO	207	51.6	20.8	53.6	0.0	100.0	207	-4.1	15.6	-6.3	-2.0	-0.4	-62.9	50.0
	SB 207499	437	51.8	22.1	53.6	0.0	100.0	437	-3.7	14.9	-5.1	-2.3	-0.2	-54.0	49.8
WEEK 24	PLACEBO	211	50.6	22.2	48.6	0.0	100.0	211	-4.7	15.7	-6.9	-2.6	-0.4	-62.7	50.0
	SB 207499	441	51.3	22.9	53.6	0.0	100.0	441	-4.2	14.9	-5.6	-2.8	-2.4	-65.9	41.4
WEEK 36	PLACEBO	195	48.0	21.2	48.6	0.0	100.0	195	-7.0	15.6	-9.2	-4.8	-5.8	-73.7	36.3
	SB 207499	407	50.2	23.4	47.7	0.0	100.0	407	-5.1	17.4	-6.8	-3.4	-5.8	-60.9	72.4
WEEK 48	PLACEBO	184	50.5	22.5	53.5	0.0	100.0	184	-5.3	18.2	-7.9	-2.6	-5.8	-61.8	45.7
	SB 207499	401	49.8	23.4	48.5	0.0	100.0	401	-5.2	17.6	-6.9	-3.5	-5.9	-66.2	44.8
WEEK 72	PLACEBO	171	50.6	21.7	53.6	0.0	100.0	171	-5.3	17.5	-8.0	-2.7	-2.6	-63.4	49.9
	SB 207499	379	49.8	24.2	47.7	0.0	100.0	379	-4.9	18.9	-6.8	-3.0	-5.9	-60.2	58.3
WEEK 96	PLACEBO	156	49.6	21.8	51.7	0.0	100.0	156	-6.2	16.4	-8.8	-3.6	-5.9	-63.4	38.0
	SB 207499	323	49.8	24.4	48.3	0.0	100.0	323	-4.6	18.9	-6.7	-2.5	-2.7	-62.2	51.7
WEEK 120	PLACEBO	144	50.3	22.3	48.7	0.0	100.0	144	-5.6	18.4	-8.6	-2.5	-1.1	-75.2	43.9
	SB 207499	290	50.4	25.3	51.1	0.0	100.0	290	-4.9	19.8	-7.2	-2.6	-2.6	-62.2	51.8
WEEK 144	PLACEBO	69	50.2	22.5	48.4	0.0	100.0	69	-3.8	19.1	-8.4	0.8	-0.4	-78.9	42.9
	SB 207499	139	49.6	23.7	51.8	0.0	100.0	139	-4.7	18.1	-7.8	-1.7	-5.2	-62.6	39.6
ENDPOINT	PLACEBO	212	51.5	22.0	48.7	0.0	100.0	212	-3.9	17.5	-6.3	-1.6	-1.5	-78.9	49.9
	SB 207499	453	51.4	25.3	53.5	0.0	100.0	453	-4.2	20.5	-6.1	-2.3	-0.9	-62.6	72.4

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION

TABLE 14.10B

DESCRIPTIVE STATISTICS FOR CHANGE FROM DAY 1 OF STUDY 040 IN ACTIVITIES SCORE OF THE SGRQ BY WEEK - PATIENTS RANDOMIZED TO PLACEBO
IN STUDIES 042/091
PROTOCOL 040

WEEKLY ASSESSMENT							CHANGE FROM DAY 1							
WEEK	N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
DAY 1	212	50.5	22.2	48.6	0.0	100.0	.	.	.	.	.	.	.	.
WEEK 12	196	47.9	21.2	48.5	0.0	100.0	196	-2.2	12.7	-4.0	-0.4	0.0	-38.2	49.4
WEEK 24	184	50.2	22.7	53.5	0.0	100.0	184	-0.5	15.3	-2.7	1.7	0.0	-37.7	63.9
WEEK 48	171	50.4	21.6	53.5	0.0	100.0	171	-0.1	14.6	-2.3	2.2	0.0	-50.4	47.7
WEEK 72	155	49.5	21.9	50.3	0.0	100.0	155	-1.5	15.8	-4.0	1.0	-0.1	-39.2	56.4
WEEK 96	143	50.3	22.4	48.5	0.0	100.0	143	-0.2	17.6	-3.1	2.7	0.0	-66.3	69.4
WEEK 120	69	50.2	22.5	48.4	0.0	100.0	69	3.0	16.2	-0.9	6.9	0.0	-33.9	60.1
ENDPOINT	212	51.4	22.1	48.6	0.0	100.0	212	0.9	16.0	-1.3	3.1	0.0	-66.3	60.1

1. WEEK IS RELATIVE TO VISIT 1 OF STUDY 040

SB 207499

TABLE 14.11A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN OVERALL DYSPNEA SCORE BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

		WEEKLY ASSESSMENT						CHANGE FROM BASELINE							
	PRIOR TREATMENT	N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
BASELINE	PLACEBO	235	3.18	1.28	3.00	0.00	8.00	.	.	.	.	.	.	.	.
	SB 207499	470	3.19	1.49	3.00	0.00	9.00	.	.	.	.	.	.	.	.
WEEK 2	PLACEBO	235	3.28	1.44	3.00	0.00	8.00	235	0.10	1.28	-0.06	0.27	0.00	-6.00	5.00
	SB 207499	470	3.14	1.49	3.00	0.00	9.00	470	-0.05	1.28	-0.16	0.07	0.00	-7.00	5.00
WEEK 4	PLACEBO	235	3.10	1.36	3.00	0.00	7.00	235	-0.08	1.16	-0.23	0.07	0.00	-4.00	4.50
	SB 207499	470	3.05	1.41	3.00	0.00	9.00	470	-0.14	1.29	-0.25	-0.02	0.00	-6.00	5.00
WEEK 8	PLACEBO	235	3.08	1.46	3.00	0.00	7.00	235	-0.11	1.36	-0.28	0.07	0.00	-4.00	5.00
	SB 207499	470	2.88	1.38	3.00	0.00	9.00	470	-0.31	1.31	-0.43	-0.19	0.00	-6.00	7.00
WEEK 12	PLACEBO	234	3.06	1.58	3.00	0.00	10.00	234	-0.12	1.46	-0.31	0.07	0.00	-4.00	6.00
	SB 207499	470	2.90	1.43	3.00	0.00	9.00	470	-0.29	1.34	-0.41	-0.17	0.00	-5.50	5.00
WEEK 16	PLACEBO	234	2.98	1.40	3.00	0.00	8.00	234	-0.18	1.34	-0.36	-0.01	0.00	-4.00	5.50
	SB 207499	470	2.92	1.44	3.00	0.00	8.00	470	-0.27	1.45	-0.40	-0.13	0.00	-7.00	5.00
WEEK 20	PLACEBO	235	2.98	1.38	3.00	0.00	8.00	235	-0.20	1.27	-0.36	-0.04	0.00	-5.00	4.50
	SB 207499	470	2.87	1.49	3.00	0.00	9.00	470	-0.32	1.37	-0.44	-0.20	0.00	-6.50	5.00
WEEK 24	PLACEBO	235	2.88	1.46	3.00	0.00	8.00	235	-0.30	1.43	-0.48	-0.12	0.00	-7.00	5.00
	SB 207499	470	2.86	1.51	3.00	0.00	8.50	470	-0.33	1.45	-0.46	-0.20	0.00	-7.00	5.50
WEEK 26	PLACEBO	227	2.76	1.29	3.00	0.00	8.00	227	-0.42	1.24	-0.58	-0.26	0.00	-5.00	4.00
	SB 207499	458	2.79	1.38	3.00	0.00	9.00	458	-0.42	1.44	-0.55	-0.29	0.00	-6.00	5.00
WEEK 28	PLACEBO	218	2.85	1.35	3.00	0.00	8.00	218	-0.36	1.33	-0.54	-0.19	0.00	-5.00	4.50
	SB 207499	459	2.81	1.38	3.00	0.00	9.00	459	-0.40	1.46	-0.53	-0.26	0.00	-7.00	5.00
WEEK 32	PLACEBO	213	2.98	1.42	3.00	0.00	8.00	213	-0.22	1.33	-0.40	-0.04	0.00	-4.00	6.00
	SB 207499	451	2.84	1.38	3.00	0.00	8.00	451	-0.36	1.43	-0.49	-0.22	0.00	-7.00	4.50
WEEK 36	PLACEBO	208	2.92	1.39	3.00	0.00	9.50	208	-0.28	1.27	-0.45	-0.11	0.00	-4.00	5.00
	SB 207499	443	2.82	1.47	3.00	0.00	9.00	443	-0.37	1.51	-0.51	-0.23	0.00	-7.00	5.00
WEEK 40	PLACEBO	201	2.95	1.37	3.00	0.00	8.00	201	-0.23	1.30	-0.41	-0.05	0.00	-4.00	4.00
	SB 207499	438	2.90	1.51	3.00	0.00	10.00	438	-0.31	1.51	-0.45	-0.16	0.00	-6.50	7.00
WEEK 44	PLACEBO	197	2.87	1.33	3.00	0.00	7.50	197	-0.30	1.29	-0.48	-0.12	0.00	-4.00	4.00

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION

SB 207499

TABLE 14.11A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN OVERALL DYSPNEA SCORE BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

		WEEKLY ASSESSMENT						CHANGE FROM BASELINE							
WEEK	PRIOR TREATMENT	N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
WEEK 44	SB 207499	435	2.90	1.54	3.00	0.00	9.00	435	-0.31	1.48	-0.45	-0.17	0.00	-7.00	5.00
WEEK 48	PLACEBO	193	2.97	1.43	3.00	0.00	7.50	193	-0.24	1.38	-0.43	-0.04	0.00	-5.00	4.00
	SB 207499	428	2.91	1.58	3.00	0.00	9.00	428	-0.28	1.55	-0.42	-0.13	0.00	-6.00	5.50
WEEK 52	PLACEBO	191	3.08	1.62	3.00	0.00	9.50	191	-0.13	1.51	-0.34	0.09	0.00	-5.00	6.00
	SB 207499	422	2.94	1.52	3.00	0.00	8.50	422	-0.24	1.47	-0.38	-0.10	0.00	-6.00	5.00
WEEK 56	PLACEBO	187	2.94	1.26	3.00	0.00	8.00	187	-0.27	1.24	-0.45	-0.10	0.00	-5.00	4.00
	SB 207499	418	2.89	1.52	3.00	0.00	9.00	418	-0.26	1.46	-0.40	-0.12	0.00	-6.00	5.00
WEEK 60	PLACEBO	187	2.90	1.40	3.00	0.00	9.00	187	-0.31	1.43	-0.52	-0.10	0.00	-5.00	6.00
	SB 207499	413	2.87	1.54	3.00	0.00	9.00	413	-0.29	1.51	-0.44	-0.15	0.00	-7.00	5.00
WEEK 64	PLACEBO	184	3.04	1.43	3.00	0.00	8.00	184	-0.17	1.40	-0.37	0.04	0.00	-5.00	5.00
	SB 207499	407	2.91	1.59	3.00	0.00	10.00	407	-0.25	1.54	-0.40	-0.10	0.00	-6.00	6.00
WEEK 68	PLACEBO	184	2.88	1.29	3.00	0.00	8.00	184	-0.32	1.20	-0.50	-0.15	0.00	-5.00	4.00
	SB 207499	406	2.90	1.54	3.00	0.00	10.00	406	-0.27	1.47	-0.42	-0.13	0.00	-6.00	5.50
WEEK 72	PLACEBO	184	2.98	1.44	3.00	0.00	9.00	184	-0.23	1.36	-0.43	-0.03	0.00	-4.00	7.00
	SB 207499	402	2.85	1.58	3.00	0.00	10.00	402	-0.31	1.50	-0.46	-0.16	0.00	-6.00	5.50
WEEK 76	PLACEBO	180	3.02	1.43	3.00	0.00	8.00	180	-0.18	1.27	-0.37	0.00	0.00	-4.00	4.00
	SB 207499	385	2.95	1.60	3.00	0.00	10.00	385	-0.18	1.52	-0.33	-0.03	0.00	-6.00	6.00
WEEK 80	PLACEBO	172	2.93	1.49	3.00	0.00	9.00	172	-0.26	1.47	-0.48	-0.04	0.00	-6.00	7.00
	SB 207499	367	2.97	1.62	3.00	0.00	10.00	367	-0.14	1.49	-0.30	0.01	0.00	-5.00	5.50
WEEK 84	PLACEBO	174	2.98	1.53	3.00	0.00	9.00	174	-0.21	1.53	-0.44	0.02	0.00	-5.00	6.00
	SB 207499	373	2.97	1.65	3.00	0.00	10.00	373	-0.19	1.60	-0.36	-0.03	0.00	-6.00	5.50
WEEK 88	PLACEBO	141	3.10	1.37	3.00	0.00	8.00	141	-0.02	1.37	-0.25	0.20	0.00	-5.00	5.00
	SB 207499	311	2.96	1.62	3.00	0.00	10.00	311	-0.13	1.56	-0.30	0.05	0.00	-6.00	5.50
WEEK 92	PLACEBO	140	3.03	1.36	3.00	0.00	7.00	140	-0.08	1.38	-0.31	0.15	0.00	-5.00	4.00
	SB 207499	299	3.05	1.71	3.00	0.00	10.00	299	-0.02	1.56	-0.20	0.16	0.00	-6.00	5.50
WEEK 96	PLACEBO	171	3.02	1.61	3.00	0.00	10.00	171	-0.16	1.60	-0.40	0.08	0.00	-5.00	7.00
	SB 207499	359	2.94	1.69	3.00	0.00	10.00	359	-0.21	1.61	-0.38	-0.04	0.00	-6.00	6.00

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION

TABLE 14.11A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN OVERALL DYSPNEA SCORE BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

		WEEKLY ASSESSMENT						CHANGE FROM BASELINE							
WEEK	PRIOR TREATMENT	N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
WEEK 100	PLACEBO	100	3.16	1.78	3.00	0.00	9.00	100	0.11	1.77	-0.24	0.46	0.00	-5.00	7.00
	SB 207499	199	2.99	1.67	3.00	0.00	10.00	199	-0.05	1.63	-0.27	0.18	0.00	-6.00	6.00
WEEK 104	PLACEBO	99	2.85	1.46	3.00	0.00	7.00	99	-0.21	1.51	-0.51	0.10	0.00	-5.50	4.00
	SB 207499	193	2.90	1.66	3.00	0.00	10.00	193	-0.07	1.62	-0.30	0.16	0.00	-6.00	5.50
WEEK 108	PLACEBO	163	2.99	1.54	3.00	0.00	9.00	163	-0.21	1.61	-0.45	0.04	0.00	-5.50	5.00
	SB 207499	336	2.87	1.57	3.00	0.00	10.00	336	-0.26	1.59	-0.43	-0.09	0.00	-6.00	6.00
WEEK 112	PLACEBO	53	3.28	1.63	3.00	0.00	7.00	53	0.08	1.44	-0.32	0.47	0.00	-4.00	3.00
	SB 207499	97	2.80	1.64	3.00	0.00	10.00	97	-0.15	1.78	-0.51	0.21	0.00	-8.50	5.50
WEEK 116	PLACEBO	52	3.16	1.81	3.00	0.00	7.00	52	-0.03	1.76	-0.52	0.46	0.00	-5.50	4.00
	SB 207499	95	2.96	1.86	3.00	0.00	10.00	95	0.02	1.80	-0.34	0.39	0.00	-5.00	5.50
WEEK 120	PLACEBO	160	3.15	1.69	3.00	0.00	10.00	160	-0.03	1.76	-0.31	0.24	0.00	-5.00	7.00
	SB 207499	332	2.96	1.72	3.00	0.00	10.00	332	-0.19	1.70	-0.37	-0.00	0.00	-5.00	10.00
WEEK 132	PLACEBO	130	3.28	1.72	3.00	0.00	10.00	130	0.09	1.77	-0.22	0.40	0.00	-5.00	7.00
	SB 207499	277	3.01	1.65	3.00	0.00	10.00	277	-0.13	1.59	-0.32	0.05	0.00	-6.00	6.00
WEEK 144	PLACEBO	91	3.32	1.77	3.00	0.00	10.00	91	0.21	2.00	-0.20	0.63	0.00	-5.00	7.00
	SB 207499	191	3.05	1.76	3.00	0.00	10.00	191	-0.06	1.70	-0.30	0.19	0.00	-6.00	6.00
WEEK 156	PLACEBO	36	3.46	1.33	3.00	0.00	7.00	36	0.02	1.59	-0.52	0.56	0.00	-5.00	3.00
	SB 207499	58	3.49	1.56	3.00	0.00	9.00	58	-0.08	1.56	-0.49	0.33	0.00	-4.50	5.00
ENDPOINT	PLACEBO	235	3.23	1.65	3.00	0.00	10.00	235	0.05	1.70	-0.17	0.27	0.00	-5.00	7.00
	SB 207499	470	3.00	1.74	3.00	0.00	10.00	470	-0.19	1.65	-0.34	-0.04	0.00	-6.00	6.00

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION

TABLE 14.11B

DESCRIPTIVE STATISTICS FOR CHANGE FROM DAY 1 OF STUDY 040 IN OVERALL DYSPNEA SCORE BY WEEK - PATIENTS RANDOMIZED TO PLACEBO
IN STUDIES 042/091
PROTOCOL 040

WEEKLY ASSESSMENT							CHANGE FROM DAY 1							
WEEK	N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
DAY 1	234	2.87	1.46	3.00	0.00	8.00	.	.	.	.	.	.	.	.
WEEK 2	226	2.75	1.29	3.00	0.00	8.00	226	-0.12	1.06	-0.26	0.02	0.00	-5.50	2.50
WEEK 4	217	2.85	1.35	3.00	0.00	8.00	217	-0.03	1.05	-0.17	0.11	0.00	-5.50	2.00
WEEK 8	212	2.97	1.42	3.00	0.00	8.00	212	0.09	1.09	-0.06	0.24	0.00	-4.00	7.00
WEEK 12	207	2.91	1.39	3.00	0.00	9.50	207	0.02	1.09	-0.13	0.17	0.00	-4.00	4.00
WEEK 16	200	2.94	1.37	3.00	0.00	8.00	200	0.08	1.17	-0.08	0.24	0.00	-4.00	5.00
WEEK 20	196	2.87	1.34	3.00	0.00	7.50	196	0.03	1.11	-0.13	0.19	0.00	-4.00	4.00
WEEK 24	192	2.97	1.43	3.00	0.00	7.50	192	0.11	1.11	-0.05	0.26	0.00	-3.00	6.00
WEEK 28	190	3.08	1.63	3.00	0.00	9.50	190	0.24	1.26	0.06	0.42	0.00	-3.00	7.00
WEEK 32	186	2.94	1.26	3.00	0.00	8.00	186	0.08	1.01	-0.07	0.23	0.00	-4.00	2.00
WEEK 36	186	2.90	1.40	3.00	0.00	9.00	186	0.05	1.16	-0.12	0.21	0.00	-4.00	3.00
WEEK 40	183	3.04	1.43	3.00	0.00	8.00	183	0.17	1.14	0.00	0.33	0.00	-4.00	4.00
WEEK 44	183	2.88	1.30	3.00	0.00	8.00	183	0.01	1.18	-0.17	0.18	0.00	-4.00	3.00
WEEK 48	183	2.96	1.44	3.00	0.00	9.00	183	0.09	1.20	-0.09	0.26	0.00	-5.00	6.00
WEEK 52	179	3.01	1.43	3.00	0.00	8.00	179	0.13	1.29	-0.06	0.32	0.00	-4.00	3.00
WEEK 56	171	2.93	1.49	3.00	0.00	9.00	171	0.05	1.24	-0.13	0.24	0.00	-4.00	6.00
WEEK 60	173	2.98	1.53	3.00	0.00	9.00	173	0.10	1.11	-0.07	0.27	0.00	-3.00	5.00
WEEK 64	141	3.10	1.37	3.00	0.00	8.00	141	0.25	1.12	0.06	0.44	0.00	-3.00	4.00
WEEK 68	140	3.03	1.36	3.00	0.00	7.00	140	0.19	1.10	0.01	0.38	0.00	-3.00	3.00
WEEK 72	170	3.03	1.61	3.00	0.00	10.00	170	0.15	1.31	-0.05	0.35	0.00	-4.00	5.00
WEEK 76	100	3.16	1.78	3.00	0.00	9.00	100	0.40	1.33	0.13	0.66	0.00	-3.00	5.00

1. WEEK IS RELATIVE TO VISIT 1 OF STUDY 040

TABLE 14.11B

DESCRIPTIVE STATISTICS FOR CHANGE FROM DAY 1 OF STUDY 040 IN OVERALL DYSPNEA SCORE BY WEEK - PATIENTS RANDOMIZED TO PLACEBO
IN STUDIES 042/091
PROTOCOL 040

WEEKLY ASSESSMENT							CHANGE FROM DAY 1							
WEEK	N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
WEEK 80	99	2.85	1.46	3.00	0.00	7.00	99	0.06	1.26	-0.19	0.32	0.00	-6.00	3.00
WEEK 84	162	2.99	1.55	3.00	0.00	9.00	162	0.09	1.31	-0.12	0.29	0.00	-6.00	4.00
WEEK 88	53	3.28	1.63	3.00	0.00	7.00	53	0.56	1.27	0.21	0.91	0.50	-2.00	3.00
WEEK 92	52	3.16	1.81	3.00	0.00	7.00	52	0.44	1.76	-0.05	0.93	0.25	-6.00	4.00
WEEK 96	159	3.15	1.70	3.00	0.00	10.00	159	0.23	1.38	0.02	0.45	0.00	-3.00	5.00
WEEK 108	129	3.29	1.73	3.00	0.00	10.00	129	0.42	1.51	0.16	0.68	0.00	-5.00	6.00
WEEK 120	91	3.32	1.77	3.00	0.00	10.00	91	0.54	1.70	0.19	0.89	0.00	-5.00	5.00
WEEK 132	36	3.46	1.33	3.00	0.00	7.00	36	0.55	1.58	0.02	1.08	0.25	-2.00	3.00
ENDPOINT	234	3.23	1.66	3.00	0.00	10.00	234	0.36	1.44	0.18	0.55	0.00	-5.00	5.00

1. WEEK IS RELATIVE TO VISIT 1 OF STUDY 040

TABLE 14.12A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN POST-EXERCISE DYSPNEA SCORE BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

		WEEKLY ASSESSMENT						CHANGE FROM BASELINE							
	PRIOR TREATMENT	N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
BASELINE	PLACEBO	208	3.67	1.68	3.00	0.00	10.00	.	.	.	.	.	.	.	.
	SB 207499	439	3.82	1.83	3.50	0.00	9.00	.	.	.	.	.	.	.	.
WEEK 4	PLACEBO	207	3.60	1.67	3.00	0.00	9.00	207	-0.07	1.31	-0.25	0.11	0.00	-5.00	5.00
	SB 207499	434	3.53	1.70	3.00	0.00	10.00	434	-0.29	1.42	-0.42	-0.16	0.00	-6.00	4.50
WEEK 8	PLACEBO	203	3.53	1.66	3.00	0.00	9.00	203	-0.16	1.28	-0.33	0.02	0.00	-5.00	3.60
	SB 207499	436	3.38	1.66	3.00	0.00	10.00	436	-0.43	1.47	-0.57	-0.30	0.00	-7.00	6.00
WEEK 12	PLACEBO	204	3.61	1.79	3.00	0.00	9.00	204	-0.07	1.50	-0.27	0.14	0.00	-5.00	5.00
	SB 207499	434	3.46	1.69	3.00	0.00	10.00	434	-0.35	1.44	-0.49	-0.22	0.00	-6.00	7.00
WEEK 16	PLACEBO	204	3.59	1.71	3.00	0.00	8.00	204	-0.07	1.37	-0.26	0.11	0.00	-4.00	4.00
	SB 207499	423	3.44	1.70	3.00	0.00	10.00	423	-0.36	1.52	-0.51	-0.22	0.00	-7.00	5.00
WEEK 20	PLACEBO	204	3.54	1.76	3.00	0.00	9.00	204	-0.11	1.45	-0.31	0.09	0.00	-4.00	4.00
	SB 207499	432	3.39	1.77	3.00	0.00	10.00	432	-0.41	1.50	-0.55	-0.27	0.00	-6.00	5.00
WEEK 24	PLACEBO	206	3.48	1.73	3.00	0.00	9.00	206	-0.17	1.33	-0.36	0.01	0.00	-5.00	4.00
	SB 207499	436	3.40	1.71	3.00	0.00	10.00	436	-0.41	1.52	-0.56	-0.27	0.00	-6.00	5.00
WEEK 36	PLACEBO	201	3.47	1.64	3.00	0.00	9.00	201	-0.20	1.54	-0.42	0.01	0.00	-6.00	4.50
	SB 207499	432	3.39	1.72	3.00	0.00	9.50	432	-0.43	1.69	-0.59	-0.27	0.00	-7.50	4.00
WEEK 48	PLACEBO	176	3.45	1.64	3.00	0.00	8.00	176	-0.25	1.58	-0.48	-0.01	0.00	-7.00	5.00
	SB 207499	405	3.45	1.72	3.00	0.00	9.00	405	-0.35	1.72	-0.52	-0.18	0.00	-7.00	5.00
WEEK 60	PLACEBO	174	3.50	1.67	3.00	0.00	10.00	174	-0.21	1.72	-0.46	0.05	0.00	-6.00	7.00
	SB 207499	385	3.39	1.78	3.00	0.00	10.00	385	-0.41	1.73	-0.59	-0.24	0.00	-6.00	5.00
WEEK 72	PLACEBO	167	3.46	1.59	3.00	0.00	8.00	167	-0.25	1.70	-0.51	0.01	0.00	-6.00	4.00
	SB 207499	372	3.44	1.77	3.00	0.00	9.00	372	-0.35	1.73	-0.53	-0.17	0.00	-6.00	5.00
WEEK 84	PLACEBO	153	3.56	1.72	3.00	0.00	9.50	153	-0.18	1.89	-0.49	0.12	0.00	-6.00	6.50
	SB 207499	333	3.61	1.90	3.00	0.00	10.00	333	-0.16	1.89	-0.37	0.04	0.00	-6.50	6.00
WEEK 96	PLACEBO	157	3.67	1.76	3.00	0.00	10.00	157	-0.09	1.89	-0.39	0.20	0.00	-6.00	5.50
	SB 207499	334	3.54	1.90	3.00	0.00	10.00	334	-0.26	1.88	-0.46	-0.06	0.00	-8.00	6.00
WEEK 108	PLACEBO	145	3.59	1.77	3.00	0.00	8.50	145	-0.11	1.90	-0.42	0.21	0.00	-7.00	6.00

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION

TABLE 14.12A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN POST-EXERCISE DYSPNEA SCORE BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

		WEEKLY ASSESSMENT						CHANGE FROM BASELINE							
WEEK	PRIOR TREATMENT	N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
WEEK 108	SB 207499	307	3.54	1.81	3.00	0.00	10.00	307	-0.29	1.92	-0.51	-0.08	0.00	-6.00	7.00
WEEK 120	PLACEBO	143	3.58	1.97	3.00	0.00	10.00	143	-0.19	2.07	-0.53	0.15	0.00	-8.00	5.00
	SB 207499	303	3.53	1.79	3.00	0.00	8.50	303	-0.26	1.90	-0.47	-0.04	0.00	-8.00	5.50
WEEK 132	PLACEBO	110	3.73	1.70	3.00	0.00	8.00	110	-0.01	2.01	-0.39	0.37	0.00	-6.00	7.00
	SB 207499	239	3.64	1.85	3.00	0.00	9.00	239	-0.23	1.98	-0.48	0.02	0.00	-7.00	5.00
WEEK 144	PLACEBO	80	3.79	1.65	3.25	0.00	7.50	80	0.35	2.06	-0.11	0.81	0.00	-4.00	7.00
	SB 207499	173	3.61	1.87	3.50	0.00	9.00	173	-0.05	1.89	-0.34	0.23	0.00	-7.00	5.00
WEEK 156	PLACEBO	33	4.17	1.75	3.50	2.00	8.00	33	0.59	2.53	-0.31	1.49	0.50	-4.00	5.00
	SB 207499	53	4.15	1.82	4.00	1.00	9.00	53	0.16	2.15	-0.44	0.75	0.00	-7.00	5.00
ENDPOINT	PLACEBO	208	3.85	1.89	3.50	0.00	10.00	208	0.18	1.99	-0.09	0.45	0.00	-6.00	7.00
	SB 207499	439	3.63	1.93	3.30	0.00	10.00	439	-0.19	1.95	-0.37	-0.00	0.00	-7.00	6.00

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION

TABLE 14.12B

DESCRIPTIVE STATISTICS FOR CHANGE FROM DAY 1 OF STUDY 040 IN POST-EXERCISE DYSPNEA SCORE BY WEEK - PATIENTS RANDOMIZED TO PLACEBO
IN STUDIES 042/091
PROTOCOL 040

WEEKLY ASSESSMENT							CHANGE FROM DAY 1							
WEEK	N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
DAY 1	205	3.47	1.71	3.00	0.00	9.00	.	.	.	.	.	.	.	.
WEEK 12	198	3.46	1.65	3.00	0.00	9.00	198	-0.03	1.23	-0.20	0.14	0.00	-5.00	5.00
WEEK 24	174	3.42	1.62	3.00	0.00	8.00	174	-0.01	1.30	-0.20	0.19	0.00	-6.00	5.00
WEEK 36	172	3.51	1.66	3.00	0.00	10.00	172	0.03	1.43	-0.18	0.25	0.00	-6.00	7.00
WEEK 48	166	3.45	1.59	3.00	0.00	8.00	166	0.01	1.43	-0.21	0.23	0.00	-5.00	6.00
WEEK 60	152	3.55	1.71	3.00	0.00	9.50	152	0.06	1.67	-0.21	0.33	0.00	-6.00	6.50
WEEK 72	156	3.65	1.76	3.00	0.00	10.00	156	0.16	1.71	-0.11	0.43	0.00	-6.00	6.00
WEEK 84	145	3.59	1.77	3.00	0.00	8.50	145	0.11	1.65	-0.16	0.38	0.00	-6.00	6.00
WEEK 96	143	3.58	1.97	3.00	0.00	10.00	143	0.11	1.90	-0.21	0.42	0.00	-7.00	6.00
WEEK 108	109	3.72	1.70	3.00	0.00	8.00	109	0.21	1.86	-0.14	0.57	0.00	-7.00	7.00
WEEK 120	79	3.78	1.66	3.00	0.00	7.50	79	0.60	1.82	0.19	1.00	0.50	-4.00	7.00
WEEK 132	33	4.17	1.75	3.50	2.00	8.00	33	0.81	2.29	-0.00	1.63	1.00	-5.00	5.50
ENDPOINT	205	3.84	1.88	3.50	0.00	10.00	205	0.37	1.76	0.13	0.61	0.00	-7.00	7.00

1. WEEK IS RELATIVE TO VISIT 1 OF STUDY 040

TABLE 14.13A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN DISTANCE WALKED BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

WEEK	PRIOR TREATMENT	WEEKLY ASSESSMENT						CHANGE FROM BASELINE							
		N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
BASELINE	PLACEBO	207	411.3	138.2	420.0	32.0	730.0	.	.	.	.	.	.	.	.
	SB 207499	441	435.0	143.1	430.0	23.0	960.0	.	.	.	.	.	.	.	.
WEEK 4	PLACEBO	206	419.4	144.7	409.0	24.0	775.0	206	9.1	85.4	-2.7	20.8	10.0	-360	405.0
	SB 207499	433	437.3	141.3	435.0	27.0	920.0	433	1.7	87.5	-6.6	10.0	0.0	-460	396.0
WEEK 8	PLACEBO	202	427.9	140.7	432.5	36.0	775.0	202	16.4	90.0	3.9	28.9	12.5	-340	600.0
	SB 207499	435	439.6	138.8	435.0	30.0	950.0	435	4.1	76.1	-3.1	11.3	2.0	-440	371.0
WEEK 12	PLACEBO	203	432.2	142.3	430.0	26.0	800.0	203	22.5	80.6	11.3	33.6	16.0	-250	335.0
	SB 207499	435	439.5	137.7	432.0	28.0	917.0	435	3.0	90.5	-5.5	11.5	5.0	-490	403.0
WEEK 16	PLACEBO	203	429.3	145.4	432.0	37.0	836.0	203	16.5	85.6	4.7	28.4	15.0	-350	320.0
	SB 207499	425	439.1	134.3	430.0	20.0	982.0	425	3.6	85.2	-4.6	11.7	7.0	-400	356.0
WEEK 20	PLACEBO	203	430.8	139.2	422.0	41.0	800.0	203	17.9	87.4	5.8	30.0	10.0	-200	400.0
	SB 207499	434	445.2	135.8	440.0	30.0	845.0	434	8.5	86.7	0.3	16.6	10.5	-350	346.0
WEEK 24	PLACEBO	205	428.1	137.0	430.0	2.0	770.0	205	15.7	90.2	3.3	28.1	20.0	-503	335.0
	SB 207499	438	443.4	131.8	440.0	28.0	914.0	438	8.1	90.7	-0.4	16.6	10.0	-400	457.0
WEEK 36	PLACEBO	203	426.7	144.3	430.0	0.0	900.0	203	12.6	107.0	-2.2	27.4	13.0	-540	800.0
	SB 207499	434	428.1	142.7	430.0	0.0	915.0	434	-7.5	105.5	-17.4	2.5	0.0	-537	384.0
WEEK 48	PLACEBO	178	425.5	141.5	430.0	0.0	704.0	178	7.8	94.7	-6.2	21.8	1.0	-540	267.0
	SB 207499	409	430.9	139.9	430.0	0.0	950.0	409	-7.1	96.7	-16.5	2.3	0.0	-450	473.0
WEEK 60	PLACEBO	173	417.7	131.7	410.0	0.0	745.0	173	2.2	102.0	-13.1	17.5	0.0	-540	294.0
	SB 207499	390	428.0	147.4	427.5	0.0	982.0	390	-10.3	111.3	-21.4	0.7	0.0	-480	390.0
WEEK 72	PLACEBO	169	422.0	135.8	420.0	0.0	710.0	169	-1.3	104.8	-17.2	14.7	6.0	-580	265.0
	SB 207499	376	421.9	138.0	420.0	0.0	850.0	376	-13.7	108.1	-24.6	-2.7	0.0	-500	385.0
WEEK 84	PLACEBO	153	421.5	143.5	420.0	0.0	791.0	153	5.1	102.8	-11.3	21.5	11.0	-450	229.0
	SB 207499	336	427.4	146.0	426.0	0.0	970.0	336	-10.5	126.7	-24.1	3.1	0.0	-480	740.0
WEEK 96	PLACEBO	159	422.4	134.8	420.0	0.0	840.0	159	6.6	102.0	-9.4	22.6	12.0	-400	305.0
	SB 207499	336	420.8	143.2	420.0	0.0	905.0	336	-11.3	123.5	-24.5	2.0	0.0	-654	488.0
WEEK 108	PLACEBO	146	421.7	131.1	404.0	0.0	710.0	146	9.2	118.3	-10.2	28.5	14.5	-550	323.0

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION

TABLE 14.13A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN DISTANCE WALKED BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

		WEEKLY ASSESSMENT						CHANGE FROM BASELINE							
WEEK	PRIOR TREATMENT	N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
WEEK 108	SB 207499	312	419.8	148.1	410.0	0.0	980.0	312	-7.9	129.1	-22.3	6.5	0.0	-736	530.0
WEEK 120	PLACEBO	146	421.3	133.7	420.0	0.0	700.0	146	17.5	95.1	1.9	33.0	20.0	-349	260.0
	SB 207499	304	424.7	139.8	420.0	0.0	886.0	304	-5.3	125.3	-19.5	8.8	0.0	-550	485.0
WEEK 132	PLACEBO	110	421.9	132.4	417.5	0.0	810.0	110	16.1	121.9	-6.9	39.2	27.0	-455	400.0
	SB 207499	243	417.2	150.3	410.0	0.0	917.0	243	-20.9	129.9	-37.3	-4.5	0.0	-590	300.0
WEEK 144	PLACEBO	81	407.0	152.2	400.0	0.0	710.0	81	6.1	119.7	-20.4	32.6	17.0	-540	327.0
	SB 207499	175	424.0	154.4	420.0	0.0	982.0	175	-19.0	131.4	-38.6	0.7	0.0	-600	400.0
WEEK 156	PLACEBO	34	363.4	140.6	362.5	0.0	610.0	34	-22.1	142.9	-71.9	27.8	4.0	-717	150.0
	SB 207499	52	409.6	114.3	404.0	192.0	670.0	52	-9.6	64.5	-27.5	8.4	-9.5	-170	120.0
ENDPOINT	PLACEBO	207	409.9	152.6	400.0	0.0	780.0	207	-1.4	126.6	-18.8	15.9	10.0	-717	327.0
	SB 207499	441	413.2	151.0	417.0	0.0	982.0	441	-21.8	131.6	-34.1	-9.5	0.0	-600	485.0

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION

TABLE 14.13B

DESCRIPTIVE STATISTICS FOR CHANGE FROM DAY 1 OF STUDY 040 IN DISTANCE WALKED BY WEEK - PATIENTS RANDOMIZED TO PLACEBO
IN STUDIES 042/091
PROTOCOL 040

WEEKLY ASSESSMENT							CHANGE FROM DAY 1							
WEEK	N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
DAY 1	205	429.2	140.6	428.0	2.0	840.0	.	.	.	.	.	.	.	.
WEEK 12	200	426.6	143.4	435.0	0.0	900.0	200	-4.7	103.8	-19.2	9.8	0.0	-500	580.0
WEEK 24	176	424.9	140.2	430.0	0.0	704.0	176	-11.4	105.3	-27.1	4.2	0.0	-490	478.0
WEEK 36	172	416.7	130.3	407.5	0.0	745.0	172	-18.0	97.0	-32.6	-3.4	0.0	-490	300.0
WEEK 48	169	419.7	134.3	420.0	0.0	710.0	169	-19.5	103.5	-35.2	-3.8	-5.0	-555	226.0
WEEK 60	153	417.6	144.0	420.0	0.0	791.0	153	-19.3	110.9	-37.1	-1.6	0.0	-470	258.0
WEEK 72	159	419.6	132.7	410.0	0.0	840.0	159	-15.9	120.3	-34.8	2.9	0.0	-500	330.0
WEEK 84	145	424.6	126.7	405.0	0.0	710.0	145	-11.9	119.5	-31.5	7.7	0.0	-620	292.0
WEEK 96	145	424.2	129.5	420.0	0.0	700.0	145	-7.2	106.4	-24.6	10.3	0.0	-500	368.0
WEEK 108	110	415.6	130.1	407.5	0.0	760.0	110	-1.6	123.2	-24.8	21.7	10.0	-480	368.0
WEEK 120	81	400.4	150.4	400.0	0.0	687.0	81	-17.2	130.0	-45.9	11.6	-10.0	-490	292.0
WEEK 132	34	363.4	140.6	362.5	0.0	610.0	34	-60.5	127.3	-105	-16.1	-36.0	-607	100.0
ENDPOINT	205	410.0	149.6	400.0	0.0	780.0	205	-19.1	135.5	-37.8	-0.5	-11.0	-607	478.0

1. WEEK IS RELATIVE TO VISIT 1 OF STUDY 040

TABLE 14.14A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN PHYSICAL COMPOSITE SCORE OF THE SF-36 BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

WEEK	PRIOR TREATMENT	N	WEEKLY ASSESSMENT					CHANGE FROM BASELINE							
			MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
BASELINE	PLACEBO	199	39.0	9.5	39.5	10.4	56.7	.	.	.	.	.	.	.	.
	SB 207499	409	40.4	9.2	41.1	12.2	66.2	.	.	.	.	.	.	.	.
WEEK 24	PLACEBO	187	40.9	8.9	41.3	17.0	58.6	187	1.7	8.5	0.5	2.9	1.2	-21.0	28.7
	SB 207499	386	41.4	9.4	42.5	18.0	62.6	386	0.9	7.4	0.2	1.7	0.7	-20.0	26.3
WEEK 48	PLACEBO	169	40.7	9.5	41.6	16.2	57.7	169	1.7	9.4	0.3	3.1	1.1	-32.8	27.4
	SB 207499	355	42.0	9.6	42.7	18.7	60.0	355	1.3	7.7	0.4	2.1	0.9	-17.3	25.1
WEEK 72	PLACEBO	158	41.3	9.2	43.1	14.9	57.2	158	2.4	9.7	0.8	3.9	1.6	-23.3	27.9
	SB 207499	334	43.1	9.4	44.9	15.7	60.0	334	2.3	8.4	1.4	3.3	2.0	-25.2	24.0
WEEK 96	PLACEBO	142	41.9	8.6	43.1	19.9	56.8	142	2.7	9.4	1.1	4.2	2.3	-18.2	27.1
	SB 207499	290	42.2	9.5	43.2	21.6	61.1	290	1.4	8.3	0.5	2.4	1.2	-26.2	26.8
WEEK 120	PLACEBO	135	40.7	8.8	41.8	16.3	56.9	135	1.6	9.7	-0.0	3.3	1.0	-21.5	28.3
	SB 207499	255	41.9	9.6	43.2	20.0	64.8	255	1.2	8.6	0.1	2.3	0.8	-27.5	31.1
WEEK 144	PLACEBO	66	39.9	10.1	40.6	12.2	62.1	66	0.8	9.8	-1.6	3.2	0.5	-19.0	29.3
	SB 207499	130	42.0	9.5	44.1	14.8	57.5	130	0.4	7.8	-0.9	1.8	0.1	-22.7	19.0
ENDPOINT	PLACEBO	199	40.1	9.6	41.7	12.2	62.1	199	1.1	9.1	-0.2	2.4	0.9	-19.1	29.3
	SB 207499	409	41.2	9.9	42.4	14.8	60.2	409	0.7	8.8	-0.1	1.6	0.3	-24.3	31.1

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION

TABLE 14.15A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN MENTAL COMPOSITE SCORE OF THE SF-36 BY WEEK AND
PRIOR TREATMENT IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

		WEEKLY ASSESSMENT						CHANGE FROM BASELINE							
WEEK	PRIOR TREATMENT	N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
BASELINE	PLACEBO	199	50.8	10.6	52.6	21.3	68.7	.	.	.	.	.	.	.	.
	SB 207499	409	51.1	10.7	54.5	17.1	67.8	.	.	.	.	.	.	.	.
WEEK 24	PLACEBO	187	51.4	10.3	53.4	17.8	69.4	187	0.5	8.4	-0.8	1.7	0.4	-25.8	32.1
	SB 207499	386	51.0	10.7	53.3	18.8	69.4	386	0.1	9.2	-0.8	1.0	0.0	-38.3	37.1
WEEK 48	PLACEBO	169	50.4	10.2	53.5	21.6	66.3	169	0.1	9.8	-1.4	1.6	-0.5	-31.1	35.7
	SB 207499	355	51.2	10.5	54.1	18.4	68.5	355	-0.1	8.3	-1.0	0.8	-0.9	-31.7	34.2
WEEK 72	PLACEBO	158	50.5	10.2	53.1	22.6	68.0	158	-0.3	10.4	-1.9	1.3	-0.8	-31.9	36.0
	SB 207499	334	50.7	10.7	52.7	18.8	68.7	334	-0.4	9.8	-1.5	0.6	-0.1	-34.5	32.0
WEEK 96	PLACEBO	142	49.7	10.4	51.4	22.0	68.3	142	-1.1	9.6	-2.7	0.5	-0.9	-28.0	27.5
	SB 207499	290	49.7	11.2	53.1	16.8	68.5	290	-1.1	9.9	-2.2	0.1	-0.4	-34.0	34.2
WEEK 120	PLACEBO	135	50.7	9.8	52.4	21.9	68.0	135	-0.5	10.0	-2.2	1.2	0.1	-30.0	28.5
	SB 207499	255	50.5	10.5	53.0	18.5	70.8	255	-1.1	9.8	-2.3	0.1	-1.1	-35.3	34.7
WEEK 144	PLACEBO	66	49.8	11.2	51.7	19.2	66.4	66	-2.3	10.3	-4.8	0.3	-2.4	-31.7	28.5
	SB 207499	130	50.3	10.4	52.8	19.5	66.8	130	-1.4	10.0	-3.1	0.4	-1.8	-27.4	34.9
ENDPOINT	PLACEBO	199	48.8	10.8	50.5	18.6	68.0	199	-2.0	10.8	-3.5	-0.5	-2.6	-31.7	28.5
	SB 207499	409	49.7	10.9	52.1	16.8	68.5	409	-1.4	10.1	-2.3	-0.4	-1.0	-37.7	34.9

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION

TABLE 14.16A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN PHYSICAL FUNCTIONING SCORE OF THE SF-36 BY WEEK AND
PRIOR TREATMENT IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

		WEEKLY ASSESSMENT						CHANGE FROM BASELINE							
WEEK	PRIOR TREATMENT	N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
BASELINE	PLACEBO	205	56.1	23.0	55.0	0.0	100.0	.	.	.	.	.	.	.	.
	SB 207499	437	56.6	23.2	55.0	0.0	100.0	.	.	.	.	.	.	.	.
WEEK 24	PLACEBO	203	59.3	24.5	60.0	0.0	100.0	203	3.1	18.6	0.5	5.6	2.8	-70.0	60.0
	SB 207499	432	59.9	24.6	65.0	0.0	100.0	432	3.2	17.4	1.6	4.8	0.9	-60.0	55.0
WEEK 48	PLACEBO	184	60.0	23.4	65.0	0.0	100.0	184	4.1	19.3	1.3	6.9	5.0	-55.0	70.0
	SB 207499	399	60.5	25.4	65.0	0.0	100.0	399	2.8	18.2	1.0	4.6	4.4	-75.0	55.0
WEEK 72	PLACEBO	175	59.7	23.4	65.0	0.0	100.0	175	3.8	20.6	0.7	6.9	5.0	-80.0	70.0
	SB 207499	379	60.4	25.8	65.0	0.0	100.0	379	3.3	20.7	1.2	5.4	5.0	-85.0	55.0
WEEK 96	PLACEBO	155	61.2	23.5	65.0	0.0	100.0	155	5.2	20.2	1.9	8.4	5.0	-75.0	65.0
	SB 207499	325	60.2	26.0	65.0	0.0	100.0	325	2.7	20.7	0.5	5.0	5.0	-85.0	55.0
WEEK 120	PLACEBO	147	59.1	22.7	60.0	7.1	100.0	147	2.8	22.0	-0.8	6.3	0.0	-75.0	65.0
	SB 207499	294	60.1	25.8	65.0	0.0	100.0	294	3.7	20.8	1.3	6.1	2.5	-70.0	63.9
WEEK 144	PLACEBO	69	56.2	24.3	60.0	0.0	100.0	69	-1.4	24.0	-7.2	4.3	0.0	-50.0	63.9
	SB 207499	143	62.2	24.5	65.0	0.0	100.0	143	2.5	20.9	-1.0	5.9	0.0	-85.0	60.0
ENDPOINT	PLACEBO	205	57.6	24.0	60.0	0.0	100.0	205	1.4	20.4	-1.4	4.3	0.0	-75.0	65.0
	SB 207499	437	58.8	26.8	65.0	0.0	100.0	437	2.2	22.1	0.1	4.3	0.0	-90.0	75.0

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION

TABLE 14.17A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN PHYSICAL ROLE FUNCTIONING SCORE OF THE SF-36 BY WEEK AND
PRIOR TREATMENT IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

WEEK	PRIOR TREATMENT	N	WEEKLY ASSESSMENT					N	CHANGE FROM BASELINE						
			MEAN	STD	MEDIAN	MIN	MAX		MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
BASELINE	PLACEBO	203	50.7	41.6	50.0	0.0	100.0	.	.	.	.	.	.	.	.
	SB 207499	423	58.7	41.4	75.0	0.0	100.0	.	.	.	.	.	.	.	.
WEEK 24	PLACEBO	197	59.3	40.3	75.0	0.0	100.0	197	7.2	40.9	1.4	12.9	0.0	-100.0	100.0
	SB 207499	411	62.5	40.9	75.0	0.0	100.0	411	3.1	37.5	-0.5	6.8	0.0	-100.0	100.0
WEEK 48	PLACEBO	174	58.4	42.7	75.0	0.0	100.0	174	7.9	46.9	0.8	14.9	0.0	-100.0	100.0
	SB 207499	377	65.2	41.1	100.0	0.0	100.0	377	5.3	38.9	1.4	9.2	0.0	-100.0	100.0
WEEK 72	PLACEBO	166	63.7	40.9	75.0	0.0	100.0	166	12.3	43.1	5.7	19.0	0.0	-100.0	100.0
	SB 207499	358	71.2	38.5	100.0	0.0	100.0	358	11.7	41.9	7.3	16.0	0.0	-100.0	100.0
WEEK 96	PLACEBO	149	63.4	42.1	75.0	0.0	100.0	149	12.4	49.2	4.5	20.4	0.0	-100.0	100.0
	SB 207499	308	63.0	42.2	87.5	0.0	100.0	308	3.9	44.4	-1.1	8.9	0.0	-100.0	100.0
WEEK 120	PLACEBO	142	60.6	41.9	75.0	0.0	100.0	142	7.9	48.2	-0.1	15.9	0.0	-100.0	100.0
	SB 207499	271	66.9	40.4	100.0	0.0	100.0	271	6.0	42.2	0.9	11.0	0.0	-100.0	100.0
WEEK 144	PLACEBO	68	53.3	43.2	50.0	0.0	100.0	68	0.7	47.3	-10.7	12.2	0.0	-100.0	100.0
	SB 207499	136	60.9	43.8	75.0	0.0	100.0	136	-5.5	43.8	-12.9	2.0	0.0	-100.0	100.0
ENDPOINT	PLACEBO	203	54.6	42.8	50.0	0.0	100.0	203	3.8	46.7	-2.7	10.3	0.0	-100.0	100.0
	SB 207499	423	60.6	42.7	75.0	0.0	100.0	423	1.9	44.8	-2.4	6.1	0.0	-100.0	100.0

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION

TABLE 14.18A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN EMOTIONAL ROLE FUNCTIONING SCORE OF THE SF-36 BY WEEK AND
PRIOR TREATMENT IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

		WEEKLY ASSESSMENT						CHANGE FROM BASELINE							
WEEK	PRIOR TREATMENT	N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
BASELINE	PLACEBO	204	70.4	40.6	100.0	0.0	100.0	.	.	.	.	.	.	.	.
	SB 207499	429	70.4	39.6	100.0	0.0	100.0	.	.	.	.	.	.	.	.
WEEK 24	PLACEBO	196	70.2	40.1	100.0	0.0	100.0	196	-1.2	37.8	-6.5	4.1	0.0	-100.0	100.0
	SB 207499	411	73.6	39.3	100.0	0.0	100.0	411	3.3	40.2	-0.6	7.2	0.0	-100.0	100.0
WEEK 48	PLACEBO	183	73.4	38.6	100.0	0.0	100.0	183	3.5	44.5	-3.0	10.0	0.0	-100.0	100.0
	SB 207499	385	74.3	39.2	100.0	0.0	100.0	385	2.6	36.3	-1.0	6.2	0.0	-100.0	100.0
WEEK 72	PLACEBO	167	75.3	37.7	100.0	0.0	100.0	167	5.2	44.4	-1.6	12.0	0.0	-100.0	100.0
	SB 207499	361	75.6	37.7	100.0	0.0	100.0	361	4.6	41.4	0.3	8.9	0.0	-100.0	100.0
WEEK 96	PLACEBO	149	75.4	38.6	100.0	0.0	100.0	149	2.7	43.9	-4.4	9.8	0.0	-100.0	100.0
	SB 207499	312	71.8	40.7	100.0	0.0	100.0	312	1.3	41.7	-3.4	5.9	0.0	-100.0	100.0
WEEK 120	PLACEBO	140	78.6	35.6	100.0	0.0	100.0	140	7.6	45.8	-0.0	15.3	0.0	-100.0	100.0
	SB 207499	285	73.4	39.9	100.0	0.0	100.0	285	1.1	43.0	-3.9	6.1	0.0	-100.0	100.0
WEEK 144	PLACEBO	66	69.2	42.3	100.0	0.0	100.0	66	-7.6	42.5	-18.0	2.9	0.0	-100.0	100.0
	SB 207499	140	71.3	41.5	100.0	0.0	100.0	140	-3.7	38.9	-10.2	2.8	0.0	-100.0	100.0
ENDPOINT	PLACEBO	204	67.5	42.0	100.0	0.0	100.0	204	-2.9	47.6	-9.5	3.6	0.0	-100.0	100.0
	SB 207499	429	68.6	42.3	100.0	0.0	100.0	429	-1.7	40.8	-5.6	2.1	0.0	-100.0	100.0

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION

TABLE 14.19A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN SOCIAL FUNCTIONING SCORE OF THE SF-36 BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

WEEK	PRIOR TREATMENT	N	WEEKLY ASSESSMENT					CHANGE FROM BASELINE							
			MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
BASELINE	PLACEBO	206	79.7	22.4	87.5	0.0	100.0	.	.	.	.	.	.	.	.
	SB 207499	438	81.1	22.6	87.5	0.0	100.0	.	.	.	.	.	.	.	.
WEEK 24	PLACEBO	204	81.5	21.1	87.5	12.5	100.0	204	1.7	19.5	-1.0	4.4	0.0	-62.5	62.5
	SB 207499	432	80.4	23.6	87.5	0.0	100.0	432	-0.8	20.4	-2.7	1.2	0.0	-87.5	75.0
WEEK 48	PLACEBO	188	79.6	22.7	87.5	0.0	100.0	188	-0.2	24.2	-3.7	3.3	0.0	-62.5	75.0
	SB 207499	404	81.7	23.3	87.5	0.0	100.0	404	-0.2	18.9	-2.0	1.7	0.0	-62.5	62.5
WEEK 72	PLACEBO	176	79.0	21.6	87.5	12.5	100.0	176	-1.1	24.8	-4.8	2.5	0.0	-87.5	62.5
	SB 207499	382	79.4	25.4	87.5	0.0	100.0	382	-1.6	22.1	-3.8	0.6	0.0	-100.0	75.0
WEEK 96	PLACEBO	158	78.6	23.6	87.5	12.5	100.0	158	-2.5	22.4	-6.1	1.0	0.0	-75.0	50.0
	SB 207499	326	77.4	26.3	87.5	0.0	100.0	326	-3.8	21.5	-6.2	-1.5	0.0	-100.0	62.5
WEEK 120	PLACEBO	147	79.3	21.8	75.0	25.0	100.0	147	-1.5	23.5	-5.4	2.3	0.0	-62.5	75.0
	SB 207499	298	79.2	24.7	87.5	0.0	100.0	298	-1.8	19.7	-4.1	0.4	0.0	-75.0	62.5
WEEK 144	PLACEBO	70	76.3	25.5	75.0	0.0	100.0	70	-4.8	25.0	-10.8	1.1	0.0	-62.5	62.5
	SB 207499	142	80.7	22.8	87.5	12.5	100.0	142	-4.0	20.0	-7.3	-0.6	0.0	-75.0	62.5
ENDPOINT	PLACEBO	206	75.8	24.3	75.0	0.0	100.0	206	-3.8	24.2	-7.2	-0.5	0.0	-62.5	62.5
	SB 207499	438	77.3	26.1	87.5	0.0	100.0	438	-3.8	21.6	-5.8	-1.8	0.0	-100.0	62.5

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION

TABLE 14.20A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN BODILY PAIN SCORE OF THE SF-36 BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

WEEK	PRIOR TREATMENT	N	WEEKLY ASSESSMENT					N	CHANGE FROM BASELINE						
			MEAN	STD	MEDIAN	MIN	MAX		MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
BASELINE	PLACEBO	205	72.8	26.7	74.0	0.0	100.0	.	.	.	.	.	.	.	.
	SB 207499	438	73.4	25.9	74.0	0.0	100.0	.	.	.	.	.	.	.	.
WEEK 24	PLACEBO	203	71.6	25.4	74.0	12.0	100.0	203	-1.1	24.3	-4.5	2.2	0.0	-78.0	78.0
	SB 207499	431	73.6	25.8	74.0	0.0	100.0	431	0.2	24.0	-2.1	2.5	0.0	-100.0	100.0
WEEK 48	PLACEBO	187	73.3	24.9	74.0	0.0	100.0	187	0.6	26.5	-3.2	4.4	0.0	-78.0	68.0
	SB 207499	402	74.0	26.3	80.0	0.0	100.0	402	-0.8	23.9	-3.1	1.6	0.0	-100.0	78.0
WEEK 72	PLACEBO	176	75.2	23.6	74.0	0.0	100.0	176	1.8	28.4	-2.5	6.0	0.0	-78.0	78.0
	SB 207499	383	76.6	25.6	84.0	0.0	100.0	383	2.9	24.6	0.5	5.4	0.0	-74.0	100.0
WEEK 96	PLACEBO	156	73.6	25.4	74.0	0.0	100.0	156	-0.5	29.1	-5.1	4.1	0.0	-90.0	88.0
	SB 207499	328	76.1	26.5	80.0	12.0	100.0	328	2.3	26.7	-0.6	5.2	0.0	-69.0	88.0
WEEK 120	PLACEBO	145	73.3	25.3	74.0	0.0	100.0	145	-0.8	29.2	-5.6	4.0	0.0	-78.0	88.0
	SB 207499	298	72.7	27.0	74.0	0.0	100.0	298	-0.3	26.6	-3.3	2.8	0.0	-78.0	78.0
WEEK 144	PLACEBO	70	71.7	27.2	74.0	12.0	100.0	70	-4.1	26.2	-10.3	2.1	0.0	-78.0	50.0
	SB 207499	143	75.5	25.5	74.0	12.0	100.0	143	-0.8	26.2	-5.1	3.5	0.0	-59.0	88.0
ENDPOINT	PLACEBO	205	70.8	26.7	74.0	0.0	100.0	205	-2.0	28.2	-5.9	1.9	0.0	-78.0	88.0
	SB 207499	438	71.2	26.9	72.0	0.0	100.0	438	-2.2	26.8	-4.8	0.3	0.0	-100.0	100.0

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION

TABLE 14.21A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN MENTAL HEALTH SCORE OF THE SF-36 BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

		WEEKLY ASSESSMENT						CHANGE FROM BASELINE							
WEEK	PRIOR TREATMENT	N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
BASELINE	PLACEBO	205	71.7	19.1	72.0	16.0	100.0	.	.	.	.	.	.	.	.
	SB 207499	436	72.6	20.1	76.0	12.0	100.0	.	.	.	.	.	.	.	.
WEEK 24	PLACEBO	203	74.1	19.4	76.0	0.0	100.0	203	2.5	14.7	0.4	4.5	4.0	-40.0	56.0
	SB 207499	429	72.2	21.3	76.0	8.0	100.0	429	-0.5	15.9	-2.0	1.0	0.0	-72.0	72.0
WEEK 48	PLACEBO	185	72.0	18.7	72.0	4.0	100.0	185	-0.0	16.2	-2.4	2.3	0.0	-40.0	64.0
	SB 207499	398	72.4	21.2	80.0	4.0	100.0	398	-0.7	16.9	-2.4	0.9	0.0	-60.0	72.0
WEEK 72	PLACEBO	174	71.2	20.5	76.0	8.0	100.0	174	-0.4	18.2	-3.1	2.3	0.0	-48.0	64.0
	SB 207499	379	72.1	21.0	76.0	0.0	100.0	379	-0.5	17.9	-2.3	1.3	0.0	-68.0	68.0
WEEK 96	PLACEBO	156	70.3	20.1	76.0	12.0	100.0	156	-2.3	17.7	-5.1	0.5	-4.0	-36.0	60.0
	SB 207499	322	70.5	22.1	76.0	0.0	100.0	322	-2.1	19.1	-4.2	-0.0	0.0	-72.0	76.0
WEEK 120	PLACEBO	146	70.0	19.8	72.0	8.0	100.0	146	-2.4	15.9	-5.0	0.2	0.0	-40.0	44.0
	SB 207499	288	71.2	21.2	76.0	4.0	100.0	288	-2.3	17.7	-4.3	-0.2	0.0	-56.0	80.0
WEEK 144	PLACEBO	70	70.2	20.3	74.0	8.0	100.0	70	-3.8	16.5	-7.8	0.1	0.0	-44.0	44.0
	SB 207499	143	73.6	19.8	76.0	0.0	100.0	143	-1.0	17.5	-3.9	1.9	0.0	-32.0	60.0
ENDPOINT	PLACEBO	205	68.5	20.8	72.0	8.0	100.0	205	-3.2	17.5	-5.6	-0.8	-4.0	-44.0	52.0
	SB 207499	436	69.7	21.3	72.0	0.0	100.0	436	-2.9	18.2	-4.6	-1.1	0.0	-72.0	80.0

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION

TABLE 14.22A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN VITALITY SCORE OF THE SF-36 BY WEEK AND PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

		WEEKLY ASSESSMENT						CHANGE FROM BASELINE							
WEEK	PRIOR TREATMENT	N	MEAN	STD	MEDIAN	MIN	MAX	N	MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
BASELINE	PLACEBO	205	54.9	21.2	55.0	5.0	100.0	.	.	.	.	.	.	.	.
	SB 207499	436	55.7	22.1	55.0	0.0	100.0	.	.	.	.	.	.	.	.
WEEK 24	PLACEBO	203	58.6	20.8	60.0	0.0	100.0	203	3.6	18.5	1.0	6.1	0.0	-40.0	70.0
	SB 207499	429	56.8	22.5	55.0	0.0	100.0	429	1.0	17.0	-0.6	2.6	0.0	-65.0	80.0
WEEK 48	PLACEBO	185	54.3	21.6	55.0	0.0	100.0	185	-1.0	21.1	-4.0	2.1	0.0	-65.0	60.0
	SB 207499	399	57.6	23.2	55.0	0.0	100.0	399	0.7	17.7	-1.1	2.4	0.0	-60.0	75.0
WEEK 72	PLACEBO	174	55.5	21.2	55.0	0.0	100.0	174	0.3	20.3	-2.8	3.3	0.0	-50.0	70.0
	SB 207499	380	57.2	22.5	55.0	0.0	100.0	380	1.1	19.0	-0.8	3.0	0.0	-55.0	65.0
WEEK 96	PLACEBO	156	54.0	21.7	55.0	0.0	100.0	156	-1.5	21.0	-4.8	1.8	-0.9	-55.0	75.0
	SB 207499	323	56.2	23.2	55.0	0.0	100.0	323	-0.3	19.8	-2.4	1.9	0.0	-55.0	65.0
WEEK 120	PLACEBO	146	55.9	20.3	55.0	0.0	100.0	146	-0.3	19.3	-3.4	2.9	0.0	-45.0	60.0
	SB 207499	289	56.2	22.7	55.0	0.0	100.0	289	-0.9	20.3	-3.3	1.4	0.0	-65.0	70.0
WEEK 144	PLACEBO	70	55.5	21.9	52.5	6.7	100.0	70	0.9	21.2	-4.2	5.9	0.0	-60.0	55.0
	SB 207499	143	59.1	20.5	60.0	5.0	100.0	143	-0.3	19.7	-3.5	3.0	0.0	-45.0	55.0
ENDPOINT	PLACEBO	205	53.9	21.8	50.0	5.0	100.0	205	-1.1	20.4	-3.9	1.7	0.0	-60.0	75.0
	SB 207499	436	54.3	22.9	55.0	0.0	100.0	436	-1.4	20.3	-3.3	0.5	0.0	-65.0	55.0

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION

TABLE 14.23A

DESCRIPTIVE STATISTICS FOR CHANGE FROM BASELINE IN GENERAL HEALTH PERCEPTIONS SCORE OF THE SF-36 BY WEEK AND
PRIOR TREATMENT IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

WEEK	PRIOR TREATMENT	N	WEEKLY ASSESSMENT					N	CHANGE FROM BASELINE						
			MEAN	STD	MEDIAN	MIN	MAX		MEAN	STD	LOWER 95% CI	UPPER 95% CI	MEDIAN	MIN	MAX
BASELINE	PLACEBO	205	47.2	19.7	45.0	0.0	97.0	.	.	.	.	.	.	.	.
	SB 207499	435	48.9	20.6	47.0	5.0	97.0	.	.	.	.	.	.	.	.
WEEK 24	PLACEBO	200	52.9	18.8	52.0	10.0	100.0	200	5.6	18.1	3.1	8.2	5.0	-47.0	60.0
	SB 207499	423	49.7	20.6	50.0	0.0	100.0	423	0.9	17.4	-0.8	2.6	0.0	-82.0	57.0
WEEK 48	PLACEBO	185	50.3	19.3	50.0	0.0	97.0	185	2.5	19.3	-0.4	5.3	5.0	-55.0	50.0
	SB 207499	396	51.1	21.4	50.0	0.0	100.0	396	2.1	18.0	0.3	3.8	0.0	-67.0	65.0
WEEK 72	PLACEBO	174	49.8	18.7	50.0	5.0	87.0	174	2.9	18.6	0.1	5.7	2.0	-50.0	47.0
	SB 207499	372	51.6	20.8	52.0	0.0	100.0	372	2.2	17.6	0.4	4.0	0.0	-62.0	55.0
WEEK 96	PLACEBO	156	49.2	18.5	50.0	10.0	100.0	156	1.7	19.3	-1.4	4.7	0.0	-50.0	57.0
	SB 207499	322	50.4	21.5	52.0	0.0	100.0	322	1.5	19.0	-0.6	3.6	0.0	-50.0	55.0
WEEK 120	PLACEBO	145	48.7	19.1	50.0	0.0	97.0	145	2.0	19.0	-1.1	5.2	0.0	-57.0	52.0
	SB 207499	294	49.0	20.6	50.0	0.0	100.0	294	0.1	18.2	-2.0	2.1	0.0	-47.0	52.0
WEEK 144	PLACEBO	70	48.4	20.2	47.0	0.0	100.0	70	2.8	20.4	-2.1	7.7	0.0	-47.0	60.0
	SB 207499	141	53.4	19.6	52.0	10.0	100.0	141	1.6	17.9	-1.4	4.6	0.0	-32.0	42.0
ENDPOINT	PLACEBO	205	48.0	19.2	47.0	0.0	100.0	205	0.8	18.1	-1.7	3.3	0.0	-47.0	60.0
	SB 207499	435	48.7	21.1	50.0	0.0	100.0	435	-0.2	18.3	-1.9	1.5	0.0	-52.0	55.0

1. WEEK IS RELATIVE TO BASELINE VISIT OF STUDIES 042/091
2. BASELINE IS DEFINED AS VISIT 3 OF STUDIES 042/091
3. WEEK 24 REPRESENTS END OF DOUBLE BLIND PHASE AND BEGINNING OF OPEN LABEL EXTENSION

TABLE 14.24

SUMMARY OF COPD EXACERBATIONS BY PRIOR TREATMENT IN STUDIES 042/091 - ALL PATIENTS

PROTOCOL 040

PRIOR TREATMENT	EXACERBATION LEVEL	NUMBER OF PATIENTS	NUMBER OF EXACERBATIONS
-----	-----	-----	-----
PLACEBO (N=243)	LEVEL 1	80	153
	LEVEL 2	132	412
	LEVEL 3	20	25
	TOTAL	155	590
SB 207499 (N=480)	LEVEL 1	181	359
	LEVEL 2	277	801
	LEVEL 3	35	45
	TOTAL	327	1205

TABLE 14.25

SUMMARY OF COPD EXACERBATION RATES PER PATIENT YEAR OF FOLLOW-UP BY PRIOR TREATMENT IN STUDIES 042/091 - ALL PATIENTS

PROTOCOL 040

PRIOR TREATMENT	RATE/PATIENT YEAR	95% CI
-----	-----	-----
PLACEBO	1.442	(1.330, 1.563)
SB 207499	1.380	(1.304, 1.460)

1. RATE IS CALCULATED BY POISSON REGRESSION INCLUDING ONLY EXACERBATIONS OCCURRING DURING STUDY 040

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TABLE 15.1A

SUMMARY OF STUDY MEDICATION EXPOSURE (DAYS) IN STUDY 040 BY PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

EXPOSURE	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
<= 14 Days	16 (6.6%)	15 (3.1%)	31 (4.3%)
15 - 28 Days	7 (2.9%)	6 (1.3%)	13 (1.8%)
29 - 56 Days	7 (2.9%)	8 (1.7%)	15 (2.1%)
57 - 84 Days	6 (2.5%)	7 (1.5%)	13 (1.8%)
85 - 112 Days	7 (2.9%)	6 (1.3%)	13 (1.8%)
113 - 140 Days	4 (1.6%)	3 (0.6%)	7 (1.0%)
141 - 168 Days	2 (0.8%)	4 (0.8%)	6 (0.8%)
169 - 196 Days	4 (1.6%)	5 (1.0%)	9 (1.2%)
197 - 224 Days	2 (0.8%)	8 (1.7%)	10 (1.4%)
225 - 252 Days	1 (0.4%)	5 (1.0%)	6 (0.8%)
253 - 280 Days	1 (0.4%)	4 (0.8%)	5 (0.7%)
281 - 308 Days	1 (0.4%)	2 (0.4%)	3 (0.4%)
309 - 336 Days	1 (0.4%)	5 (1.0%)	6 (0.8%)
337 - 364 Days	4 (1.6%)	9 (1.9%)	13 (1.8%)
365 - 392 Days	3 (1.2%)	9 (1.9%)	12 (1.7%)
393 - 420 Days	3 (1.2%)	7 (1.5%)	10 (1.4%)
421 - 448 Days	0	4 (0.8%)	4 (0.6%)
449 - 476 Days	1 (0.4%)	4 (0.8%)	5 (0.7%)
477 - 504 Days	2 (0.8%)	7 (1.5%)	9 (1.2%)
505 - 532 Days	1 (0.4%)	9 (1.9%)	10 (1.4%)
533 - 560 Days	4 (1.6%)	5 (1.0%)	9 (1.2%)
561 - 588 Days	3 (1.2%)	6 (1.3%)	9 (1.2%)

1. EXPOSURE= (DATE OF LAST DOSE OF STUDY MEDICATION-DATE OF FIRST DOSE OF STUDY MEDICATION IN STUDY 040)+1
2. NO ADJUSTMENTS ARE MADE FOR DOSE INTERRUPTIONS

SB 207499

TABLE 15.1A

SUMMARY OF STUDY MEDICATION EXPOSURE (DAYS) IN STUDY 040 BY PRIOR TREATMENT IN STUDIES 042/091
 PROTOCOL 040

EXPOSURE	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
589 - 616 Days	0 (0.0%)	2 (0.4%)	2 (0.3%)
617 - 644 Days	1 (0.4%)	4 (0.8%)	5 (0.7%)
645 - 672 Days	3 (1.2%)	6 (1.3%)	9 (1.2%)
673 - 700 Days	12 (4.9%)	15 (3.1%)	27 (3.7%)
701 - 728 Days	9 (3.7%)	30 (6.3%)	39 (5.4%)
729 - 756 Days	9 (3.7%)	15 (3.1%)	24 (3.3%)
757 - 784 Days	25 (10.3%)	49 (10.2%)	74 (10.2%)
785 - 812 Days	9 (3.7%)	18 (3.8%)	27 (3.7%)
813 - 840 Days	14 (5.8%)	21 (4.4%)	35 (4.8%)
841 - 868 Days	26 (10.7%)	87 (18.1%)	113 (15.6%)
869 - 896 Days	10 (4.1%)	22 (4.6%)	32 (4.4%)
897 - 924 Days	16 (6.6%)	25 (5.2%)	41 (5.7%)
925 - 952 Days	23 (9.5%)	32 (6.7%)	55 (7.6%)
953 - 980 Days	4 (1.6%)	14 (2.9%)	18 (2.5%)
981 - 1008 Days	2 (0.8%)	2 (0.4%)	4 (0.6%)

1. EXPOSURE=(DATE OF LAST DOSE OF STUDY MEDICATION-DATE OF FIRST DOSE OF STUDY MEDICATION IN STUDY 040)+1
2. NO ADJUSTMENTS ARE MADE FOR DOSE INTERRUPTIONS

TABLE 15.1B

DESCRIPTIVE STATISTICS FOR STUDY MEDICATION EXPOSURE (DAYS) IN STUDY 040 BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

Statistic	PRIOR TREATMENT		Total
	PLACEBO	SB 207499	
N	243	480	723
MEAN	614.47	663.94	647.31
STD	330.55	279.96	298.61
MEDIAN	757	766	764
MIN	1	1	1
MAX	996	996	996

1. EXPOSURE=(DATE OF LAST DOSE OF STUDY MEDICATION-DATE OF FIRST DOSE OF STUDY MEDICATION IN STUDY 040)+1
2. NO ADJUSTMENTS ARE MADE FOR DOSE INTERRUPTIONS

TABLE 15.2A

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND PRIOR TREATMENT
IN STUDIES 042/091
PROTOCOL 040

WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
TOTAL	229 (94.2%)	446 (92.9%)	675 (93.4%)
CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	155 (63.8%)	327 (68.1%)	482 (66.7%)
ABDOMINAL PAIN	50 (20.6%)	63 (13.1%)	113 (15.6%)
DIARRHEA	44 (18.1%)	51 (10.6%)	95 (13.1%)
INJURY	26 (10.7%)	62 (12.9%)	88 (12.2%)
BACK PAIN	23 (9.5%)	56 (11.7%)	79 (10.9%)
HEADACHE	32 (13.2%)	47 (9.8%)	79 (10.9%)
NAUSEA	34 (14.0%)	38 (7.9%)	72 (10.0%)
RHINITIS	28 (11.5%)	44 (9.2%)	72 (10.0%)
UPPER RESP TRACT INFECTION	20 (8.2%)	51 (10.6%)	71 (9.8%)
DYSPEPSIA	30 (12.3%)	35 (7.3%)	65 (9.0%)
INFECTION VIRAL	21 (8.6%)	39 (8.1%)	60 (8.3%)
PHARYNGITIS	15 (6.2%)	42 (8.8%)	57 (7.9%)
ARTHRALGIA	20 (8.2%)	30 (6.3%)	50 (6.9%)
COUGHING	13 (5.3%)	31 (6.5%)	44 (6.1%)
HYPERTENSION	10 (4.1%)	32 (6.7%)	42 (5.8%)
CHEST PAIN	15 (6.2%)	26 (5.4%)	41 (5.7%)
RESPIRATORY DISORDER	10 (4.1%)	28 (5.8%)	38 (5.3%)
VOMITING	15 (6.2%)	20 (4.2%)	35 (4.8%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AN ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091
5. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO THE TOTAL GROUP

TABLE 15.2A

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND PRIOR TREATMENT
IN STUDIES 042/091
PROTOCOL 040

WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
DIZZINESS	9 (3.7%)	25 (5.2%)	34 (4.7%)
URINARY TRACT INFECTION	10 (4.1%)	22 (4.6%)	32 (4.4%)
DEPRESSION	10 (4.1%)	21 (4.4%)	31 (4.3%)
HYPERGLYCEMIA	8 (3.3%)	23 (4.8%)	31 (4.3%)
INSOMNIA	8 (3.3%)	23 (4.8%)	31 (4.3%)
PAIN	9 (3.7%)	22 (4.6%)	31 (4.3%)
SINUSITIS	14 (5.8%)	16 (3.3%)	30 (4.1%)
HEMATURIA	13 (5.3%)	13 (2.7%)	26 (3.6%)
MYALGIA	13 (5.3%)	13 (2.7%)	26 (3.6%)
ANXIETY	13 (5.3%)	12 (2.5%)	25 (3.5%)
GASTROENTERITIS	11 (4.5%)	13 (2.7%)	24 (3.3%)
PNEUMONIA	10 (4.1%)	14 (2.9%)	24 (3.3%)
ASTHENIA	8 (3.3%)	15 (3.1%)	23 (3.2%)
LEUKOCYTOSIS	6 (2.5%)	17 (3.5%)	23 (3.2%)
BRONCHITIS	8 (3.3%)	14 (2.9%)	22 (3.0%)
DYSPNEA	8 (3.3%)	13 (2.7%)	21 (2.9%)
TACHYCARDIA	10 (4.1%)	11 (2.3%)	21 (2.9%)
CONSTIPATION	5 (2.1%)	15 (3.1%)	20 (2.8%)
WEIGHT DECREASE	9 (3.7%)	11 (2.3%)	20 (2.8%)
ARTHRITIS	7 (2.9%)	12 (2.5%)	19 (2.6%)

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INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND PRIOR TREATMENT
IN STUDIES 042/091
PROTOCOL 040

WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
FEVER	11 (4.5%)	8 (1.7%)	19 (2.6%)
NEOPLASM NOS	10 (4.1%)	9 (1.9%)	19 (2.6%)
ANGINA PECTORIS	7 (2.9%)	11 (2.3%)	18 (2.5%)
GASTRITIS	6 (2.5%)	12 (2.5%)	18 (2.5%)
NEURALGIA	7 (2.9%)	11 (2.3%)	18 (2.5%)
PRURITUS	4 (1.6%)	14 (2.9%)	18 (2.5%)
VERTIGO	5 (2.1%)	13 (2.7%)	18 (2.5%)
ALBUMINURIA	5 (2.1%)	12 (2.5%)	17 (2.4%)
EXTRASYSTOLES	4 (1.6%)	13 (2.7%)	17 (2.4%)
FATIGUE	8 (3.3%)	9 (1.9%)	17 (2.4%)
INFECTION	6 (2.5%)	11 (2.3%)	17 (2.4%)
PERIODONTITIS	5 (2.1%)	12 (2.5%)	17 (2.4%)
PROSTATIC DISORDER	11 (4.5%)	6 (1.3%)	17 (2.4%)
GAMMA-GT INCREASED	7 (2.9%)	9 (1.9%)	16 (2.2%)
MALAISE	10 (4.1%)	6 (1.3%)	16 (2.2%)
PYURIA	4 (1.6%)	12 (2.5%)	16 (2.2%)
CONJUNCTIVITIS	7 (2.9%)	8 (1.7%)	15 (2.1%)
HEPATIC ENZYMES INCREASED	3 (1.2%)	12 (2.5%)	15 (2.1%)
FLATULENCE	5 (2.1%)	8 (1.7%)	13 (1.8%)
BRADYCARDIA	7 (2.9%)	5 (1.0%)	12 (1.7%)

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INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND PRIOR TREATMENT
IN STUDIES 042/091
PROTOCOL 040

WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
CATARACT	6 (2.5%)	6 (1.3%)	12 (1.7%)
EXTRASYSTOLES SUPRAVENTRICULAR	5 (2.1%)	7 (1.5%)	12 (1.7%)
FIBRILLATION ATRIAL	3 (1.2%)	9 (1.9%)	12 (1.7%)
GASTROINTESTINAL DISORDER NOS	5 (2.1%)	7 (1.5%)	12 (1.7%)
GOUT	5 (2.1%)	7 (1.5%)	12 (1.7%)
SYNCOPE	4 (1.6%)	8 (1.7%)	12 (1.7%)
MELENA	5 (2.1%)	6 (1.3%)	11 (1.5%)
ANEMIA	2 (0.8%)	8 (1.7%)	10 (1.4%)
ANOREXIA	7 (2.9%)	3 (0.6%)	10 (1.4%)
EDEMA LEGS	5 (2.1%)	5 (1.0%)	10 (1.4%)
HEMOPTYSIS	3 (1.2%)	7 (1.5%)	10 (1.4%)
HEMORRHOIDS	2 (0.8%)	8 (1.7%)	10 (1.4%)
HERPES ZOSTER	2 (0.8%)	8 (1.7%)	10 (1.4%)
ECZEMA	4 (1.6%)	5 (1.0%)	9 (1.2%)
MONILIASIS	3 (1.2%)	6 (1.3%)	9 (1.2%)
RASH	4 (1.6%)	5 (1.0%)	9 (1.2%)
SKIN DISORDER	4 (1.6%)	5 (1.0%)	9 (1.2%)
DERMATITIS	2 (0.8%)	6 (1.3%)	8 (1.1%)
DIABETES MELLITUS	2 (0.8%)	6 (1.3%)	8 (1.1%)

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IN STUDIES 042/091
PROTOCOL 040

WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
DYSURIA	5 (2.1%)	3 (0.6%)	8 (1.1%)
ESOPHAGITIS	3 (1.2%)	5 (1.0%)	8 (1.1%)
GLYCOSURIA	4 (1.6%)	4 (0.8%)	8 (1.1%)
HYPERTENSION AGGRAVATED	3 (1.2%)	5 (1.0%)	8 (1.1%)
HYPERURICEMIA	3 (1.2%)	5 (1.0%)	8 (1.1%)
IMPOTENCE	2 (0.8%)	6 (1.3%)	8 (1.1%)
OTITIS EXTERNA	3 (1.2%)	5 (1.0%)	8 (1.1%)
OTITIS MEDIA	3 (1.2%)	5 (1.0%)	8 (1.1%)
PULMONARY CARCINOMA	1 (0.4%)	7 (1.5%)	8 (1.1%)
SKELETAL PAIN	2 (0.8%)	6 (1.3%)	8 (1.1%)
TOOTH ACHE	2 (0.8%)	6 (1.3%)	8 (1.1%)
URTICARIA	1 (0.4%)	7 (1.5%)	8 (1.1%)
ARRHYTHMIA	4 (1.6%)	3 (0.6%)	7 (1.0%)
CYSTITIS	2 (0.8%)	5 (1.0%)	7 (1.0%)
EDEMA DEPENDENT	3 (1.2%)	4 (0.8%)	7 (1.0%)
HEPATIC FUNCTION ABNORMAL	0 .	7 (1.5%)	7 (1.0%)
HYPERCHOLESTEROLEMIA	4 (1.6%)	3 (0.6%)	7 (1.0%)
HYPERTHYROIDISM	1 (0.4%)	6 (1.3%)	7 (1.0%)
NERVOUSNESS	5 (2.1%)	2 (0.4%)	7 (1.0%)

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IN STUDIES 042/091
PROTOCOL 040

WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
SGPT INCREASED	1 (0.4%)	6 (1.3%)	7 (1.0%)
SOMNOLENCE	4 (1.6%)	3 (0.6%)	7 (1.0%)
SPUTUM INCREASED	1 (0.4%)	6 (1.3%)	7 (1.0%)
ABSCESS	2 (0.8%)	4 (0.8%)	6 (0.8%)
ARTHROSIS	2 (0.8%)	4 (0.8%)	6 (0.8%)
CHEST PAIN PRECORDIAL	4 (1.6%)	2 (0.4%)	6 (0.8%)
CHOLELITHIASIS	2 (0.8%)	4 (0.8%)	6 (0.8%)
EAR DISORDER NOS	3 (1.2%)	3 (0.6%)	6 (0.8%)
HYPOGLYCEMIA	1 (0.4%)	5 (1.0%)	6 (0.8%)
HYPOTENSION	1 (0.4%)	5 (1.0%)	6 (0.8%)
INFECTION FUNGAL	4 (1.6%)	2 (0.4%)	6 (0.8%)
OSTEOPOROSIS	1 (0.4%)	5 (1.0%)	6 (0.8%)
POLYCYTHEMIA	0 .	6 (1.3%)	6 (0.8%)
TREMOR	3 (1.2%)	3 (0.6%)	6 (0.8%)
URINARY RETENTION	2 (0.8%)	4 (0.8%)	6 (0.8%)
BILIRUBINEMIA	1 (0.4%)	4 (0.8%)	5 (0.7%)
BLOOD UREA NITROGEN INCREASED	0 .	5 (1.0%)	5 (0.7%)
BUNDLE BRANCH BLOCK	2 (0.8%)	3 (0.6%)	5 (0.7%)
CARCINOMA	3 (1.2%)	2 (0.4%)	5 (0.7%)
CARDIAC FAILURE	2 (0.8%)	3 (0.6%)	5 (0.7%)

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INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND PRIOR TREATMENT
IN STUDIES 042/091
PROTOCOL 040

WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
CELLULITIS	1 (0.4%)	4 (0.8%)	5 (0.7%)
CEREBROVASCULAR DISORDER	1 (0.4%)	4 (0.8%)	5 (0.7%)
DYSPHAGIA	0 .	5 (1.0%)	5 (0.7%)
DYSPHONIA	1 (0.4%)	4 (0.8%)	5 (0.7%)
GASTROESOPHAGEAL REFLUX	3 (1.2%)	2 (0.4%)	5 (0.7%)
HYPERNATREMIA	1 (0.4%)	4 (0.8%)	5 (0.7%)
HYPOTENSION POSTURAL	1 (0.4%)	4 (0.8%)	5 (0.7%)
INTESTINAL OBSTRUCTION	1 (0.4%)	4 (0.8%)	5 (0.7%)
LARYNGITIS	3 (1.2%)	2 (0.4%)	5 (0.7%)
LYMPHADENOPATHY	3 (1.2%)	2 (0.4%)	5 (0.7%)
MICTURITION FREQUENCY	2 (0.8%)	3 (0.6%)	5 (0.7%)
SGOT INCREASED	0 .	5 (1.0%)	5 (0.7%)
SKIN DRY	3 (1.2%)	2 (0.4%)	5 (0.7%)
AGITATION	2 (0.8%)	2 (0.4%)	4 (0.6%)
ALLERGIC REACTION	2 (0.8%)	2 (0.4%)	4 (0.6%)
ARRHYTHMIA ATRIAL	1 (0.4%)	3 (0.6%)	4 (0.6%)
ARTHROPATHY	2 (0.8%)	2 (0.4%)	4 (0.6%)
CRAMPS LEGS	2 (0.8%)	2 (0.4%)	4 (0.6%)
EARACHE	1 (0.4%)	3 (0.6%)	4 (0.6%)

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IN STUDIES 042/091
PROTOCOL 040

WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
EPISTAXIS	1 (0.4%)	3 (0.6%)	4 (0.6%)
EYE ABNORMALITY	2 (0.8%)	2 (0.4%)	4 (0.6%)
GI HEMORRHAGE	3 (1.2%)	1 (0.2%)	4 (0.6%)
HERPES SIMPLEX	1 (0.4%)	3 (0.6%)	4 (0.6%)
HYPERTONIA	1 (0.4%)	3 (0.6%)	4 (0.6%)
INFLUENZA-LIKE SYMPTOMS	1 (0.4%)	3 (0.6%)	4 (0.6%)
MIGRAINE	2 (0.8%)	2 (0.4%)	4 (0.6%)
PALPITATION	0 .	4 (0.8%)	4 (0.6%)
PARESTHESIA	2 (0.8%)	2 (0.4%)	4 (0.6%)
SKIN ULCERATION	0 .	4 (0.8%)	4 (0.6%)
STOMATITIS	1 (0.4%)	3 (0.6%)	4 (0.6%)
SWEATING INCREASED	4 (1.6%)	0 .	4 (0.6%)
TRACHEITIS	1 (0.4%)	3 (0.6%)	4 (0.6%)
VASCULAR DISORDER	1 (0.4%)	3 (0.6%)	4 (0.6%)
ANEURYSM	1 (0.4%)	2 (0.4%)	3 (0.4%)
ANUS DISORDER	0 .	3 (0.6%)	3 (0.4%)
ARTHRITIS AGGRAVATED	2 (0.8%)	1 (0.2%)	3 (0.4%)
ASTHMA	2 (0.8%)	1 (0.2%)	3 (0.4%)
BLEPHARITIS	2 (0.8%)	1 (0.2%)	3 (0.4%)
CARDIOMEGALY	1 (0.4%)	2 (0.4%)	3 (0.4%)

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INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND PRIOR TREATMENT
IN STUDIES 042/091
PROTOCOL 040

WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
CHEST X-RAY ABNORMAL	0 .	3 (0.6%)	3 (0.4%)
CLAUDICATION INTERMITTENT	2 (0.8%)	1 (0.2%)	3 (0.4%)
CONFUSION	0 .	3 (0.6%)	3 (0.4%)
DEAFNESS	1 (0.4%)	2 (0.4%)	3 (0.4%)
DIABETES MELLITUS AGGRAVATED	0 .	3 (0.6%)	3 (0.4%)
DUODENITIS	1 (0.4%)	2 (0.4%)	3 (0.4%)
ECG ABNORMAL	1 (0.4%)	2 (0.4%)	3 (0.4%)
ECG ABNORMAL SPECIFIC	1 (0.4%)	2 (0.4%)	3 (0.4%)
HEMORRHAGE RECTUM	1 (0.4%)	2 (0.4%)	3 (0.4%)
HYPERKALEMIA	1 (0.4%)	2 (0.4%)	3 (0.4%)
HYPERLIPEMIA	0 .	3 (0.6%)	3 (0.4%)
HYPONATREMIA	2 (0.8%)	1 (0.2%)	3 (0.4%)
HYPOTHYROIDISM	0 .	3 (0.6%)	3 (0.4%)
LEUKOPENIA	1 (0.4%)	2 (0.4%)	3 (0.4%)
LIPOMA	2 (0.8%)	1 (0.2%)	3 (0.4%)
MOUTH DRY	1 (0.4%)	2 (0.4%)	3 (0.4%)
MUSCLE CONTRACTIONS INVOLUNTARY	1 (0.4%)	2 (0.4%)	3 (0.4%)
MYOCARDIAL INFARCTION	1 (0.4%)	2 (0.4%)	3 (0.4%)
PARESIS	2 (0.8%)	1 (0.2%)	3 (0.4%)

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3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091
5. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO THE TOTAL GROUP

TABLE 15.2A

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND PRIOR TREATMENT
IN STUDIES 042/091
PROTOCOL 040

WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
PERIPHERAL ISCHEMIA	2 (0.8%)	1 (0.2%)	3 (0.4%)
PHOSPHATASE ALKALINE INCREASED	0 .	3 (0.6%)	3 (0.4%)
PURPURA	1 (0.4%)	2 (0.4%)	3 (0.4%)
RASH MACULO-PAPULAR	0 .	3 (0.6%)	3 (0.4%)
RENAL FUNCTION ABNORMAL	2 (0.8%)	1 (0.2%)	3 (0.4%)
RENAL PAIN	0 .	3 (0.6%)	3 (0.4%)
RESPIRATORY INSUFFICIENCY	0 .	3 (0.6%)	3 (0.4%)
SEPSIS	1 (0.4%)	2 (0.4%)	3 (0.4%)
SKIN HYPERTROPHY	2 (0.8%)	1 (0.2%)	3 (0.4%)
TASTE PERVERSION	1 (0.4%)	2 (0.4%)	3 (0.4%)
TENDINITIS	0 .	3 (0.6%)	3 (0.4%)
THERAPEUTIC RESPONSE INCREASED	0 .	3 (0.6%)	3 (0.4%)
TINNITUS	2 (0.8%)	1 (0.2%)	3 (0.4%)
VAGINITIS	0 .	3 (0.6%)	3 (0.4%)
VEIN VARICOSE	0 .	3 (0.6%)	3 (0.4%)
VISION ABNORMAL	2 (0.8%)	1 (0.2%)	3 (0.4%)
ADENOCARCINOMA NOS	1 (0.4%)	1 (0.2%)	2 (0.3%)
ALOPECIA	0 .	2 (0.4%)	2 (0.3%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AN ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091
5. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO THE TOTAL GROUP

TABLE 15.2A

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND PRIOR TREATMENT
IN STUDIES 042/091
PROTOCOL 040

WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
ANGINA PECTORIS AGGRAVATED	0 .	2 (0.4%)	2 (0.3%)
APNEA	1 (0.4%)	1 (0.2%)	2 (0.3%)
ARTHRITIS RHEUMATOID	0 .	2 (0.4%)	2 (0.3%)
ATRIOVENTRICULAR BLOCK	0 .	2 (0.4%)	2 (0.3%)
BASAL CELL CARCINOMA	1 (0.4%)	1 (0.2%)	2 (0.3%)
BLADDER CARCINOMA	2 (0.8%)	0 .	2 (0.3%)
BONE DEVELOPMENT ABNORMAL	0 .	2 (0.4%)	2 (0.3%)
BONE DISORDER	0 .	2 (0.4%)	2 (0.3%)
BREAST NEOPLASM FEMALE	0 .	2 (0.4%)	2 (0.3%)
BURSITIS	0 .	2 (0.4%)	2 (0.3%)
CHEST PAIN SUBSTERNAL	1 (0.4%)	1 (0.2%)	2 (0.3%)
CHOLECYSTITIS	0 .	2 (0.4%)	2 (0.3%)
COLITIS	0 .	2 (0.4%)	2 (0.3%)
CONVULSIONS	0 .	2 (0.4%)	2 (0.3%)
CORONARY ARTERY DISORDER	0 .	2 (0.4%)	2 (0.3%)
DEHYDRATION	0 .	2 (0.4%)	2 (0.3%)
DERMATITIS FUNGAL	1 (0.4%)	1 (0.2%)	2 (0.3%)
DERMATITIS LICHENOID	0 .	2 (0.4%)	2 (0.3%)
DIVERTICULITIS	0 .	2 (0.4%)	2 (0.3%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AN ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091
5. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO THE TOTAL GROUP

TABLE 15.2A

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND PRIOR TREATMENT
IN STUDIES 042/091
PROTOCOL 040

WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
ENTERITIS	2 (0.8%)	0 .	2 (0.3%)
EOSINOPHILIA	0 .	2 (0.4%)	2 (0.3%)
EXTRAPYRAMIDAL DISORDER	1 (0.4%)	1 (0.2%)	2 (0.3%)
FOLLICULITIS	0 .	2 (0.4%)	2 (0.3%)
GASTRIC ULCER	0 .	2 (0.4%)	2 (0.3%)
GINGIVITIS	0 .	2 (0.4%)	2 (0.3%)
GOITRE	1 (0.4%)	1 (0.2%)	2 (0.3%)
GRANULOCYTOPENIA	0 .	2 (0.4%)	2 (0.3%)
HEMATEMESIS	0 .	2 (0.4%)	2 (0.3%)
HYPERKERATOSIS	1 (0.4%)	1 (0.2%)	2 (0.3%)
HYPOCHLOREMIA	1 (0.4%)	1 (0.2%)	2 (0.3%)
HYPOKALEMIA	2 (0.8%)	0 .	2 (0.3%)
HYPOXIA	1 (0.4%)	1 (0.2%)	2 (0.3%)
INFECTION BACTERIAL	0 .	2 (0.4%)	2 (0.3%)
IRRITABLE BOWEL SYNDROME	1 (0.4%)	1 (0.2%)	2 (0.3%)
LYMPHOPENIA	1 (0.4%)	1 (0.2%)	2 (0.3%)
MICTURITION DISORDER	1 (0.4%)	1 (0.2%)	2 (0.3%)
MYOCARDIAL ISCHEMIA	0 .	2 (0.4%)	2 (0.3%)
NEUROPATHY PERIPHERAL	0 .	2 (0.4%)	2 (0.3%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AN ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091
5. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO THE TOTAL GROUP

SB 207499

TABLE 15.2A

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND PRIOR TREATMENT
IN STUDIES 042/091
PROTOCOL 040

WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
NPN INCREASED	0 .	2 (0.4%)	2 (0.3%)
PANCREATITIS	1 (0.4%)	1 (0.2%)	2 (0.3%)
PLEURAL EFFUSION	1 (0.4%)	1 (0.2%)	2 (0.3%)
PLEURAL PAIN	0 .	2 (0.4%)	2 (0.3%)
PLEURISY	0 .	2 (0.4%)	2 (0.3%)
PYELONEPHRITIS	0 .	2 (0.4%)	2 (0.3%)
RASH ERYTHEMATOUS	1 (0.4%)	1 (0.2%)	2 (0.3%)
RENAL CALCULUS	1 (0.4%)	1 (0.2%)	2 (0.3%)
RENAL FAILURE ACUTE	0 .	2 (0.4%)	2 (0.3%)
RETINAL DISORDER	2 (0.8%)	0 .	2 (0.3%)
RIGORS	1 (0.4%)	1 (0.2%)	2 (0.3%)
TENDON DISORDER	1 (0.4%)	1 (0.2%)	2 (0.3%)
THROMBOCYTOPENIA	0 .	2 (0.4%)	2 (0.3%)
THROMBOPHLEBITIS DEEP	2 (0.8%)	0 .	2 (0.3%)
THROMBOSIS RETINAL ARTERY	0 .	2 (0.4%)	2 (0.3%)
TOOTH CARIES	2 (0.8%)	0 .	2 (0.3%)
TOOTH DISORDER	1 (0.4%)	1 (0.2%)	2 (0.3%)
URINARY INCONTINENCE	0 .	2 (0.4%)	2 (0.3%)
VEIN DISORDER	1 (0.4%)	1 (0.2%)	2 (0.3%)
VESTIBULAR DISORDER	1 (0.4%)	1 (0.2%)	2 (0.3%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER PREFERRED TERM
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4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091
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TABLE 15.2A

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND PRIOR TREATMENT
IN STUDIES 042/091
PROTOCOL 040

WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
WEIGHT INCREASE	1 (0.4%)	1 (0.2%)	2 (0.3%)
XEROPHTHALMIA	2 (0.8%)	0 .	2 (0.3%)
ALCOHOL INTOLERANCE	1 (0.4%)	0 .	1 (0.1%)
AMNESIA	0 .	1 (0.2%)	1 (0.1%)
ANEMIA HYPOCHROMIC	0 .	1 (0.2%)	1 (0.1%)
ANEMIA MACROCYTIC	1 (0.4%)	0 .	1 (0.1%)
ANGIOEDEMA	0 .	1 (0.2%)	1 (0.1%)
AORTIC STENOSIS	1 (0.4%)	0 .	1 (0.1%)
APATHY	1 (0.4%)	0 .	1 (0.1%)
APPETITE INCREASED	1 (0.4%)	0 .	1 (0.1%)
ARTERIOSCLEROSIS	0 .	1 (0.2%)	1 (0.1%)
ARTERITIS	1 (0.4%)	0 .	1 (0.1%)
ARTHRITIS RHEUMATOID AGGRAVATED	0 .	1 (0.2%)	1 (0.1%)
ATAXIA	1 (0.4%)	0 .	1 (0.1%)
BALANOPOSTHITIS	1 (0.4%)	0 .	1 (0.1%)
BLADDER CALCULUS	0 .	1 (0.2%)	1 (0.1%)
BREAST FIBROADENOSIS	0 .	1 (0.2%)	1 (0.1%)
BULLOUS ERUPTION	0 .	1 (0.2%)	1 (0.1%)
CARDIAC ARREST	0 .	1 (0.2%)	1 (0.1%)
CARDIOMYOPATHY	0 .	1 (0.2%)	1 (0.1%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER PREFERRED TERM
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4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091
5. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO THE TOTAL GROUP

SB 207499

TABLE 15.2A

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND PRIOR TREATMENT
IN STUDIES 042/091
PROTOCOL 040

WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
COLON CARCINOMA	1 (0.4%)	0 .	1 (0.1%)
COMA	0 .	1 (0.2%)	1 (0.1%)
CONCENTRATION IMPAIRED	1 (0.4%)	0 .	1 (0.1%)
CONJUNCTIVAL HEMORRHAGE	0 .	1 (0.2%)	1 (0.1%)
COR PULMONALE	0 .	1 (0.2%)	1 (0.1%)
CORNEAL ULCERATION	0 .	1 (0.2%)	1 (0.1%)
CYANOSIS	0 .	1 (0.2%)	1 (0.1%)
DEPRESSION AGGRAVATED	0 .	1 (0.2%)	1 (0.1%)
DIARRHEA BLOODY	0 .	1 (0.2%)	1 (0.1%)
DRUG LEVEL INCREASED	0 .	1 (0.2%)	1 (0.1%)
DUODENAL ULCER	0 .	1 (0.2%)	1 (0.1%)
DUPUYTREN'S CONTRACTURE	0 .	1 (0.2%)	1 (0.1%)
EDEMA	0 .	1 (0.2%)	1 (0.1%)
ENTEROCOLITIS	0 .	1 (0.2%)	1 (0.1%)
ERUCTATION	0 .	1 (0.2%)	1 (0.1%)
ERYTHROCYTES ABNORMAL	0 .	1 (0.2%)	1 (0.1%)
ESOPHAGOSPASM	1 (0.4%)	0 .	1 (0.1%)
FACE EDEMA	0 .	1 (0.2%)	1 (0.1%)
FURUNCULOSIS	1 (0.4%)	0 .	1 (0.1%)

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INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND PRIOR TREATMENT
IN STUDIES 042/091
PROTOCOL 040

WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
GASTRIC CARCINOMA	1 (0.4%)	0 .	1 (0.1%)
GI NEOPLASM MALIGNANT	0 .	1 (0.2%)	1 (0.1%)
GLAUCOMA	0 .	1 (0.2%)	1 (0.1%)
GLUCOSE TOLERANCE ABNORMAL	0 .	1 (0.2%)	1 (0.1%)
HEARING DECREASED	0 .	1 (0.2%)	1 (0.1%)
HEART VALVE DISORDERS	1 (0.4%)	0 .	1 (0.1%)
HEMANGIOMA ACQUIRED	0 .	1 (0.2%)	1 (0.1%)
HEMATOMA	0 .	1 (0.2%)	1 (0.1%)
HEMORRHAGE NOS	1 (0.4%)	0 .	1 (0.1%)
HEPATIC CIRRHOSIS	1 (0.4%)	0 .	1 (0.1%)
HEPATIC NEOPLASM	0 .	1 (0.2%)	1 (0.1%)
HEPATITIS	0 .	1 (0.2%)	1 (0.1%)
HEPATITIS INFECTIOUS	1 (0.4%)	0 .	1 (0.1%)
HOT FLUSHES	1 (0.4%)	0 .	1 (0.1%)
HYPERTENSION PULMONARY	0 .	1 (0.2%)	1 (0.1%)
HYPERTRIGLYCERIDEMIA	1 (0.4%)	0 .	1 (0.1%)
HYPERVENTILATION	1 (0.4%)	0 .	1 (0.1%)
HYPESTHESIA	1 (0.4%)	0 .	1 (0.1%)
ILEUS	0 .	1 (0.2%)	1 (0.1%)

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5. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO THE TOTAL GROUP

SB 207499

TABLE 15.2A

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND PRIOR TREATMENT
IN STUDIES 042/091
PROTOCOL 040

WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
INJECTION SITE INFLAMMATION	0 .	1 (0.2%)	1 (0.1%)
KETOSIS	0 .	1 (0.2%)	1 (0.1%)
LACTOSE INTOLERANCE	0 .	1 (0.2%)	1 (0.1%)
LIVER FATTY	0 .	1 (0.2%)	1 (0.1%)
LYMPHADENOPATHY CERVICAL	0 .	1 (0.2%)	1 (0.1%)
LYMPHANGITIS	1 (0.4%)	0 .	1 (0.1%)
LYMPHEDEMA	1 (0.4%)	0 .	1 (0.1%)
LYMPHOMA MALIGNANT	1 (0.4%)	0 .	1 (0.1%)
MACULA LUTEA DEGENERATION	1 (0.4%)	0 .	1 (0.1%)
MASTITIS MALE	1 (0.4%)	0 .	1 (0.1%)
MEGACOLON ACQUIRED	0 .	1 (0.2%)	1 (0.1%)
MELANOSIS	0 .	1 (0.2%)	1 (0.1%)
MENSTRUAL DISORDER	0 .	1 (0.2%)	1 (0.1%)
MONILIASIS GENITAL	0 .	1 (0.2%)	1 (0.1%)
MYOSITIS	1 (0.4%)	0 .	1 (0.1%)
NAIL DISORDER	1 (0.4%)	0 .	1 (0.1%)
NEOPLASM MALIGNANT	1 (0.4%)	0 .	1 (0.1%)
NERVE ROOT LESION	0 .	1 (0.2%)	1 (0.1%)
NEUROPATHY	0 .	1 (0.2%)	1 (0.1%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AN ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091
5. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO THE TOTAL GROUP

SB 207499

TABLE 15.2A

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND PRIOR TREATMENT
IN STUDIES 042/091
PROTOCOL 040

WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
NOCTURIA	0 .	1 (0.2%)	1 (0.1%)
OBESITY	1 (0.4%)	0 .	1 (0.1%)
ORCHITIS	1 (0.4%)	0 .	1 (0.1%)
OSTEONECROSIS	1 (0.4%)	0 .	1 (0.1%)
PARKINSONISM AGGRAVATED	0 .	1 (0.2%)	1 (0.1%)
PELVIC INFLAMMATION	1 (0.4%)	0 .	1 (0.1%)
PENIS DISORDER	1 (0.4%)	0 .	1 (0.1%)
PERITONITIS	0 .	1 (0.2%)	1 (0.1%)
PHLEBITIS	0 .	1 (0.2%)	1 (0.1%)
PHLEBITIS SUPERFICIAL	0 .	1 (0.2%)	1 (0.1%)
PHOTOSENSITIVITY ALLERGIC REACT	1 (0.4%)	0 .	1 (0.1%)
PNEUMONIA LOBAR	0 .	1 (0.2%)	1 (0.1%)
PROCTITIS	1 (0.4%)	0 .	1 (0.1%)
PSORIASIS	0 .	1 (0.2%)	1 (0.1%)
QT INCREASED	1 (0.4%)	0 .	1 (0.1%)
RASH PUSTULAR	0 .	1 (0.2%)	1 (0.1%)
RENAL CYST	0 .	1 (0.2%)	1 (0.1%)
RETINAL DETACHMENT	1 (0.4%)	0 .	1 (0.1%)
ROSACEA	1 (0.4%)	0 .	1 (0.1%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER PREFERRED TERM
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3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091
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TABLE 15.2A

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND PRIOR TREATMENT
IN STUDIES 042/091
PROTOCOL 040

WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
SIALOADENITIS	1 (0.4%)	0 .	1 (0.1%)
SPINE MALFORMATION	0 .	1 (0.2%)	1 (0.1%)
SUICIDE ATTEMPT	0 .	1 (0.2%)	1 (0.1%)
TACHYCARDIA SUPRAVENTRICULAR	0 .	1 (0.2%)	1 (0.1%)
TENESMUS	0 .	1 (0.2%)	1 (0.1%)
TESTIS DISORDER	0 .	1 (0.2%)	1 (0.1%)
THROMBOPHLEBITIS LEG	0 .	1 (0.2%)	1 (0.1%)
THROMBOPHLEBITIS RETINAL VEIN	0 .	1 (0.2%)	1 (0.1%)
THROMBOSIS ARTERIAL LEG	0 .	1 (0.2%)	1 (0.1%)
THYROIDITIS	1 (0.4%)	0 .	1 (0.1%)
TONGUE EDEMA	0 .	1 (0.2%)	1 (0.1%)
TRIGEMINAL NEURALGIA	1 (0.4%)	0 .	1 (0.1%)
TYMPANIC MEMBRANE PERFORATION	0 .	1 (0.2%)	1 (0.1%)
URINARY CASTS	1 (0.4%)	0 .	1 (0.1%)
URINE ABNORMAL	0 .	1 (0.2%)	1 (0.1%)
UVEITIS	0 .	1 (0.2%)	1 (0.1%)
VAGINAL HEMORRHAGE	0 .	1 (0.2%)	1 (0.1%)
VERRUCA	1 (0.4%)	0 .	1 (0.1%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AN ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091
5. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO THE TOTAL GROUP

TABLE 15.2A

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND PRIOR TREATMENT
IN STUDIES 042/091
PROTOCOL 040

WHO PREFERRED TERM	PRIOR TREATMENT		Total (N=723)
	PLACEBO (N=243)	SB 207499 (N=480)	
VISUAL FIELD DEFECT	0 .	1 (0.2%)	1 (0.1%)
WITHDRAWAL HEADACHE	0 .	1 (0.2%)	1 (0.1%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AN ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091
5. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO THE TOTAL GROUP

TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
TOTAL	TOTAL	229 (94.2%)	446 (92.9%)	675 (93.4%)
APPLICATION SITE	TOTAL	3 (1.2%)	5 (1.0%)	8 (1.1%)
	INJECTION SITE	0 .	1 (0.2%)	1 (0.1%)
	INFLAMMATION			
	OTITIS EXTERNA	3 (1.2%)	5 (1.0%)	8 (1.1%)
	TYMPANIC MEMBRANE PERFORATION	0 .	1 (0.2%)	1 (0.1%)
AUTONOMIC NERVOUS SYSTEM	TOTAL	5 (2.1%)	2 (0.4%)	7 (1.0%)
	MOUTH DRY	1 (0.4%)	2 (0.4%)	3 (0.4%)
	SWEATING INCREASED	4 (1.6%)	0 .	4 (0.6%)
BODY AS A WHOLE GENERAL	TOTAL	74 (30.5%)	130 (27.1%)	204 (28.2%)
	ALCOHOL INTOLERANCE	1 (0.4%)	0 .	1 (0.1%)
	ALLERGIC REACTION	2 (0.8%)	2 (0.4%)	4 (0.6%)
	ASTHENIA	8 (3.3%)	15 (3.1%)	23 (3.2%)
	CELLULITIS	1 (0.4%)	4 (0.8%)	5 (0.7%)
	CHEST PAIN	15 (6.2%)	26 (5.4%)	41 (5.7%)
	CHEST PAIN PRECORDIAL	4 (1.6%)	2 (0.4%)	6 (0.8%)
	CHEST PAIN SUBSTERNAL	1 (0.4%)	1 (0.2%)	2 (0.3%)
	DRUG LEVEL INCREASED	0 .	1 (0.2%)	1 (0.1%)
	EDEMA	0 .	1 (0.2%)	1 (0.1%)
	EDEMA DEPENDENT	3 (1.2%)	4 (0.8%)	7 (1.0%)
	EDEMA LEGS	5 (2.1%)	5 (1.0%)	10 (1.4%)
	FACE EDEMA	0 .	1 (0.2%)	1 (0.1%)
	FATIGUE	8 (3.3%)	9 (1.9%)	17 (2.4%)
	FEVER	11 (4.5%)	8 (1.7%)	19 (2.6%)
	HOT FLUSHES	1 (0.4%)	0 .	1 (0.1%)
	INFLUENZA-LIKE SYMPTOMS	1 (0.4%)	3 (0.6%)	4 (0.6%)
	INJURY	26 (10.7%)	62 (12.9%)	88 (12.2%)
	MALAISE	10 (4.1%)	6 (1.3%)	16 (2.2%)
	PAIN	9 (3.7%)	22 (4.6%)	31 (4.3%)
	RIGORS	1 (0.4%)	1 (0.2%)	2 (0.3%)
	THERAPEUTIC RESPONSE INCREASED	0 .	3 (0.6%)	3 (0.4%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM/PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AN ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
CARDIOVASCULAR GENERAL	TOTAL	24 (9.9%)	57 (11.9%)	81 (11.2%)
	ANEURYSM	1 (0.4%)	2 (0.4%)	3 (0.4%)
	CARDIAC FAILURE	2 (0.8%)	3 (0.6%)	5 (0.7%)
	CARDIOMEGALY	1 (0.4%)	2 (0.4%)	3 (0.4%)
	COR PULMONALE	0 .	1 (0.2%)	1 (0.1%)
	CYANOSIS	0 .	1 (0.2%)	1 (0.1%)
	ECG ABNORMAL	1 (0.4%)	2 (0.4%)	3 (0.4%)
	ECG ABNORMAL SPECIFIC	1 (0.4%)	2 (0.4%)	3 (0.4%)
	HEART VALVE DISORDERS	1 (0.4%)	0 .	1 (0.1%)
	HYPERTENSION	10 (4.1%)	32 (6.7%)	42 (5.8%)
	HYPERTENSION AGGRAVATED	3 (1.2%)	5 (1.0%)	8 (1.1%)
	HYPERTENSION PULMONARY	0 .	1 (0.2%)	1 (0.1%)
	HYPOTENSION	1 (0.4%)	5 (1.0%)	6 (0.8%)
	HYPOTENSION POSTURAL	1 (0.4%)	4 (0.8%)	5 (0.7%)
	SYNCOPE	4 (1.6%)	8 (1.7%)	12 (1.7%)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	TOTAL	58 (23.9%)	95 (19.8%)	153 (21.2%)
	ATAXIA	1 (0.4%)	0 .	1 (0.1%)
	COMA	0 .	1 (0.2%)	1 (0.1%)
	CONVULSIONS	0 .	2 (0.4%)	2 (0.3%)
	DIZZINESS	9 (3.7%)	25 (5.2%)	34 (4.7%)
	DYSPHONIA	1 (0.4%)	4 (0.8%)	5 (0.7%)
	EXTRAPYRAMIDAL DISORDER	1 (0.4%)	1 (0.2%)	2 (0.3%)
	HEADACHE	32 (13.2%)	47 (9.8%)	79 (10.9%)
	HYPERTONIA	1 (0.4%)	3 (0.6%)	4 (0.6%)
	HYPESTHESIA	1 (0.4%)	0 .	1 (0.1%)
	MIGRAINE	2 (0.8%)	2 (0.4%)	4 (0.6%)
	MUSCLE CONTRACTIONS INVOLUNTARY	1 (0.4%)	2 (0.4%)	3 (0.4%)
	NERVE ROOT LESION	0 .	1 (0.2%)	1 (0.1%)
	NEURALGIA	7 (2.9%)	11 (2.3%)	18 (2.5%)
	NEUROPATHY	0 .	1 (0.2%)	1 (0.1%)
	NEUROPATHY PERIPHERAL	0 .	2 (0.4%)	2 (0.3%)
	PARESIS	2 (0.8%)	1 (0.2%)	3 (0.4%)
	PARESTHESIA	2 (0.8%)	2 (0.4%)	4 (0.6%)

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TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	PARKINSONISM AGGRAVATED	0 .	1 (0.2%)	1 (0.1%)
	TREMOR	3 (1.2%)	3 (0.6%)	6 (0.8%)
	TRIGEMINAL NEURALGIA	1 (0.4%)	0 .	1 (0.1%)
	VERTIGO	5 (2.1%)	13 (2.7%)	18 (2.5%)
	WITHDRAWAL HEADACHE	0 .	1 (0.2%)	1 (0.1%)
COLLAGEN	TOTAL	0 .	3 (0.6%)	3 (0.4%)
	ARTHRITIS RHEUMATOID	0 .	2 (0.4%)	2 (0.3%)
	ARTHRITIS RHEUMATOID AGGRAVATED	0 .	1 (0.2%)	1 (0.1%)
ENDOCRINE	TOTAL	4 (1.6%)	9 (1.9%)	13 (1.8%)
	GOITRE	1 (0.4%)	1 (0.2%)	2 (0.3%)
	HYPERTHYROIDISM	1 (0.4%)	6 (1.3%)	7 (1.0%)
	HYPOTHYROIDISM	0 .	3 (0.6%)	3 (0.4%)
	MASTITIS MALE	1 (0.4%)	0 .	1 (0.1%)
	SIALOADENITIS	1 (0.4%)	0 .	1 (0.1%)
	THYROIDITIS	1 (0.4%)	0 .	1 (0.1%)
FETAL	TOTAL	0 .	1 (0.2%)	1 (0.1%)
	SPINE MALFORMATION	0 .	1 (0.2%)	1 (0.1%)
GASTROINTESTINAL SYSTEM	TOTAL	134 (55.1%)	196 (40.8%)	330 (45.6%)
	ABDOMINAL PAIN	50 (20.6%)	63 (13.1%)	113 (15.6%)
	ANOREXIA	7 (2.9%)	3 (0.6%)	10 (1.4%)
	ANUS DISORDER	0 .	3 (0.6%)	3 (0.4%)
	APPETITE INCREASED	1 (0.4%)	0 .	1 (0.1%)
	COLITIS	0 .	2 (0.4%)	2 (0.3%)
	CONSTIPATION	5 (2.1%)	15 (3.1%)	20 (2.8%)
	DIARRHEA	44 (18.1%)	51 (10.6%)	95 (13.1%)
	DIARRHEA BLOODY	0 .	1 (0.2%)	1 (0.1%)
	DIVERTICULITIS	0 .	2 (0.4%)	2 (0.3%)
	DUODENAL ULCER	0 .	1 (0.2%)	1 (0.1%)
	DUODENITIS	1 (0.4%)	2 (0.4%)	3 (0.4%)
	DYSPEPSIA	30 (12.3%)	35 (7.3%)	65 (9.0%)
	DYSPHAGIA	0 .	5 (1.0%)	5 (0.7%)
	ENTERITIS	2 (0.8%)	0 .	2 (0.3%)
	ENTEROCOLITIS	0 .	1 (0.2%)	1 (0.1%)

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TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
GASTROINTESTINAL SYSTEM	ERUCTATION	0	1 (0.2%)	1 (0.1%)
	ESOPHAGITIS	3 (1.2%)	5 (1.0%)	8 (1.1%)
	ESOPHAGOSPASM	1 (0.4%)	0	1 (0.1%)
	FLATULENCE	5 (2.1%)	8 (1.7%)	13 (1.8%)
	GASTRIC ULCER	0	2 (0.4%)	2 (0.3%)
	GASTRITIS	6 (2.5%)	12 (2.5%)	18 (2.5%)
	GASTROENTERITIS	11 (4.5%)	13 (2.7%)	24 (3.3%)
	GASTROESOPHAGEAL REFLUX	3 (1.2%)	2 (0.4%)	5 (0.7%)
	GASTROINTESTINAL DISORDER NOS	5 (2.1%)	7 (1.5%)	12 (1.7%)
	GI HEMORRHAGE	3 (1.2%)	1 (0.2%)	4 (0.6%)
	GINGIVITIS	0	2 (0.4%)	2 (0.3%)
	HEMATEMESIS	0	2 (0.4%)	2 (0.3%)
	HEMORRHAGE RECTUM	1 (0.4%)	2 (0.4%)	3 (0.4%)
	HEMORRHOIDS	2 (0.8%)	8 (1.7%)	10 (1.4%)
	ILEUS	0	1 (0.2%)	1 (0.1%)
	INTESTINAL OBSTRUCTION	1 (0.4%)	4 (0.8%)	5 (0.7%)
	IRRITABLE BOWEL SYNDROME	1 (0.4%)	1 (0.2%)	2 (0.3%)
	LACTOSE INTOLERANCE	0	1 (0.2%)	1 (0.1%)
	MEGACOLON ACQUIRED	0	1 (0.2%)	1 (0.1%)
	MELENA	5 (2.1%)	6 (1.3%)	11 (1.5%)
	NAUSEA	34 (14.0%)	38 (7.9%)	72 (10.0%)
	PANCREATITIS	1 (0.4%)	1 (0.2%)	2 (0.3%)
	PERIODONTITIS	5 (2.1%)	12 (2.5%)	17 (2.4%)
	PERITONITIS	0	1 (0.2%)	1 (0.1%)
	PROCTITIS	1 (0.4%)	0	1 (0.1%)
	STOMATITIS	1 (0.4%)	3 (0.6%)	4 (0.6%)
	TENESMUS	0	1 (0.2%)	1 (0.1%)
	TONGUE EDEMA	0	1 (0.2%)	1 (0.1%)
	TOOTH ACHE	2 (0.8%)	6 (1.3%)	8 (1.1%)
	TOOTH CARIES	2 (0.8%)	0	2 (0.3%)
	TOOTH DISORDER	1 (0.4%)	1 (0.2%)	2 (0.3%)
	VOMITING	15 (6.2%)	20 (4.2%)	35 (4.8%)
HEARING AND VESTIBULAR	TOTAL	8 (3.3%)	9 (1.9%)	17 (2.4%)
	DEAFNESS	1 (0.4%)	2 (0.4%)	3 (0.4%)
	EAR DISORDER NOS	3 (1.2%)	3 (0.6%)	6 (0.8%)

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TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
HEARING AND VESTIBULAR	EARACHE	1 (0.4%)	3 (0.6%)	4 (0.6%)
	HEARING DECREASED	0 .	1 (0.2%)	1 (0.1%)
	TINNITUS	2 (0.8%)	1 (0.2%)	3 (0.4%)
	VESTIBULAR DISORDER	1 (0.4%)	1 (0.2%)	2 (0.3%)
HEART RATE AND RHYTHM	TOTAL	31 (12.8%)	48 (10.0%)	79 (10.9%)
	ARRHYTHMIA	4 (1.6%)	3 (0.6%)	7 (1.0%)
	ARRHYTHMIA ATRIAL	1 (0.4%)	3 (0.6%)	4 (0.6%)
	ATRIOVENTRICULAR BLOCK	0 .	2 (0.4%)	2 (0.3%)
	BRADYCARDIA	7 (2.9%)	5 (1.0%)	12 (1.7%)
	BUNDLE BRANCH BLOCK	2 (0.8%)	3 (0.6%)	5 (0.7%)
	CARDIAC ARREST	0 .	1 (0.2%)	1 (0.1%)
	EXTRASYSTOLES	4 (1.6%)	13 (2.7%)	17 (2.4%)
	EXTRASYSTOLES SUPRAVENTRICULAR	5 (2.1%)	7 (1.5%)	12 (1.7%)
	FIBRILLATION ATRIAL	3 (1.2%)	9 (1.9%)	12 (1.7%)
	PALPITATION	0 .	4 (0.8%)	4 (0.6%)
	QT INCREASED	1 (0.4%)	0 .	1 (0.1%)
	TACHYCARDIA	10 (4.1%)	11 (2.3%)	21 (2.9%)
	TACHYCARDIA SUPRAVENTRICULAR	0 .	1 (0.2%)	1 (0.1%)
LIVER AND BILIARY SYSTEM	TOTAL	13 (5.3%)	36 (7.5%)	49 (6.8%)
	BILIRUBINEMIA	1 (0.4%)	4 (0.8%)	5 (0.7%)
	CHOLECYSTITIS	0 .	2 (0.4%)	2 (0.3%)
	CHOLELITHIASIS	2 (0.8%)	4 (0.8%)	6 (0.8%)
	GAMMA-GT INCREASED	7 (2.9%)	9 (1.9%)	16 (2.2%)
	HEPATIC CIRRHOSIS	1 (0.4%)	0 .	1 (0.1%)
	HEPATIC ENZYMES INCREASED	3 (1.2%)	12 (2.5%)	15 (2.1%)
	HEPATIC FUNCTION ABNORMAL	0 .	7 (1.5%)	7 (1.0%)
	HEPATITIS	0 .	1 (0.2%)	1 (0.1%)
	HEPATITIS INFECTIOUS	1 (0.4%)	0 .	1 (0.1%)
	LIVER FATTY	0 .	1 (0.2%)	1 (0.1%)
	SGOT INCREASED	0 .	5 (1.0%)	5 (0.7%)
	SGPT INCREASED	1 (0.4%)	6 (1.3%)	7 (1.0%)

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TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
METABOLIC AND NUTRITIONAL	TOTAL	36 (14.8%)	69 (14.4%)	105 (14.5%)
	BLOOD UREA NITROGEN INCREASED	0 .	5 (1.0%)	5 (0.7%)
	DEHYDRATION	0 .	2 (0.4%)	2 (0.3%)
	DIABETES MELLITUS	2 (0.8%)	6 (1.3%)	8 (1.1%)
	DIABETES MELLITUS AGGRAVATED	0 .	3 (0.6%)	3 (0.4%)
	GLUCOSE TOLERANCE ABNORMAL	0 .	1 (0.2%)	1 (0.1%)
	GLYCOSURIA	4 (1.6%)	4 (0.8%)	8 (1.1%)
	GOUT	5 (2.1%)	7 (1.5%)	12 (1.7%)
	HYPERCHOLESTEROLEMIA	4 (1.6%)	3 (0.6%)	7 (1.0%)
	HYPERGLYCEMIA	8 (3.3%)	23 (4.8%)	31 (4.3%)
	HYPERKALEMIA	1 (0.4%)	2 (0.4%)	3 (0.4%)
	HYPERLIPEMIA	0 .	3 (0.6%)	3 (0.4%)
	HYPERNATREMIA	1 (0.4%)	4 (0.8%)	5 (0.7%)
	HYPERTRIGLYCERIDEMIA	1 (0.4%)	0 .	1 (0.1%)
	HYPERURICEMIA	3 (1.2%)	5 (1.0%)	8 (1.1%)
	HYPOCHLOREMIA	1 (0.4%)	1 (0.2%)	2 (0.3%)
	HYPOGLYCEMIA	1 (0.4%)	5 (1.0%)	6 (0.8%)
	HYPOKALEMIA	2 (0.8%)	0 .	2 (0.3%)
	HYPONATREMIA	2 (0.8%)	1 (0.2%)	3 (0.4%)
	KETOSIS	0 .	1 (0.2%)	1 (0.1%)
	NPN INCREASED	0 .	2 (0.4%)	2 (0.3%)
	OBESITY	1 (0.4%)	0 .	1 (0.1%)
	PHOSPHATASE ALKALINE INCREASED	0 .	3 (0.6%)	3 (0.4%)
	WEIGHT DECREASE	9 (3.7%)	11 (2.3%)	20 (2.8%)
	WEIGHT INCREASE	1 (0.4%)	1 (0.2%)	2 (0.3%)
MUSCULOSKELETAL SYSTEM	TOTAL	60 (24.7%)	107 (22.3%)	167 (23.1%)
	ARTHRALGIA	20 (8.2%)	30 (6.3%)	50 (6.9%)
	ARTHRITIS	7 (2.9%)	12 (2.5%)	19 (2.6%)
	ARTHRITIS AGGRAVATED	2 (0.8%)	1 (0.2%)	3 (0.4%)
	ARTHROPATHY	2 (0.8%)	2 (0.4%)	4 (0.6%)
	ARTHROSIS	2 (0.8%)	4 (0.8%)	6 (0.8%)
	BACK PAIN	23 (9.5%)	56 (11.7%)	79 (10.9%)
	BONE DEVELOPMENT ABNORMAL	0 .	2 (0.4%)	2 (0.3%)

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TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
MUSCULOSKELETAL SYSTEM	BONE DISORDER	0 .	2 (0.4%)	2 (0.3%)
	BURSITIS	0 .	2 (0.4%)	2 (0.3%)
	DUPUYTREN'S CONTRACTURE	0 .	1 (0.2%)	1 (0.1%)
	MYALGIA	13 (5.3%)	13 (2.7%)	26 (3.6%)
	MYOSITIS	1 (0.4%)	0 .	1 (0.1%)
	OSTEONECROSIS	1 (0.4%)	0 .	1 (0.1%)
	OSTEOPOROSIS	1 (0.4%)	5 (1.0%)	6 (0.8%)
	SKELETAL PAIN	2 (0.8%)	6 (1.3%)	8 (1.1%)
	TENDINITIS	0 .	3 (0.6%)	3 (0.4%)
	TENDON DISORDER	1 (0.4%)	1 (0.2%)	2 (0.3%)
	TOTAL	9 (3.7%)	18 (3.8%)	27 (3.7%)
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	ANGINA PECTORIS	7 (2.9%)	11 (2.3%)	18 (2.5%)
	ANGINA PECTORIS AGGRAVATED	0 .	2 (0.4%)	2 (0.3%)
	AORTIC STENOSIS	1 (0.4%)	0 .	1 (0.1%)
	CARDIOMYOPATHY	0 .	1 (0.2%)	1 (0.1%)
	CORONARY ARTERY DISORDER	0 .	2 (0.4%)	2 (0.3%)
	MYOCARDIAL INFARCTION	1 (0.4%)	2 (0.4%)	3 (0.4%)
	MYOCARDIAL ISCHEMIA	0 .	2 (0.4%)	2 (0.3%)
	TOTAL	23 (9.5%)	27 (5.6%)	50 (6.9%)
	ADENOCARCINOMA NOS	1 (0.4%)	1 (0.2%)	2 (0.3%)
NEOPLASM	BASAL CELL CARCINOMA	1 (0.4%)	1 (0.2%)	2 (0.3%)
	BLADDER CARCINOMA	2 (0.8%)	0 .	2 (0.3%)
	BREAST FIBROADENOSIS	0 .	1 (0.2%)	1 (0.1%)
	BREAST NEOPLASM FEMALE	0 .	2 (0.4%)	2 (0.3%)
	CARCINOMA	3 (1.2%)	2 (0.4%)	5 (0.7%)
	COLON CARCINOMA	1 (0.4%)	0 .	1 (0.1%)
	GASTRIC CARCINOMA	1 (0.4%)	0 .	1 (0.1%)
	GI NEOPLASM MALIGNANT	0 .	1 (0.2%)	1 (0.1%)
	HEMANGIOMA ACQUIRED	0 .	1 (0.2%)	1 (0.1%)
	HEPATIC NEOPLASM	0 .	1 (0.2%)	1 (0.1%)
	LIPOMA	2 (0.8%)	1 (0.2%)	3 (0.4%)
	LYMPHOMA MALIGNANT	1 (0.4%)	0 .	1 (0.1%)
	NEOPLASM MALIGNANT	1 (0.4%)	0 .	1 (0.1%)
	TOTAL	23 (9.5%)	27 (5.6%)	50 (6.9%)
	ADENOCARCINOMA NOS	1 (0.4%)	1 (0.2%)	2 (0.3%)
	BASAL CELL CARCINOMA	1 (0.4%)	1 (0.2%)	2 (0.3%)
	BLADDER CARCINOMA	2 (0.8%)	0 .	2 (0.3%)
	BREAST FIBROADENOSIS	0 .	1 (0.2%)	1 (0.1%)
	BREAST NEOPLASM FEMALE	0 .	2 (0.4%)	2 (0.3%)
	CARCINOMA	3 (1.2%)	2 (0.4%)	5 (0.7%)
	COLON CARCINOMA	1 (0.4%)	0 .	1 (0.1%)
	GASTRIC CARCINOMA	1 (0.4%)	0 .	1 (0.1%)
	GI NEOPLASM MALIGNANT	0 .	1 (0.2%)	1 (0.1%)
	HEMANGIOMA ACQUIRED	0 .	1 (0.2%)	1 (0.1%)
	HEPATIC NEOPLASM	0 .	1 (0.2%)	1 (0.1%)
	LIPOMA	2 (0.8%)	1 (0.2%)	3 (0.4%)
	LYMPHOMA MALIGNANT	1 (0.4%)	0 .	1 (0.1%)
	NEOPLASM MALIGNANT	1 (0.4%)	0 .	1 (0.1%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM/PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AN ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
NEOPLASM	NEOPLASM NOS	10 (4.1%)	9 (1.9%)	19 (2.6%)
	PULMONARY CARCINOMA	1 (0.4%)	7 (1.5%)	8 (1.1%)
PLATELET BLEEDING AND CLOTTING	TOTAL	1 (0.4%)	5 (1.0%)	6 (0.8%)
	HEMATOMA	0 .	1 (0.2%)	1 (0.1%)
	PURPURA	1 (0.4%)	2 (0.4%)	3 (0.4%)
	THROMBOCYTOPENIA	0 .	2 (0.4%)	2 (0.3%)
PSYCHIATRIC	TOTAL	35 (14.4%)	57 (11.9%)	92 (12.7%)
	AGITATION	2 (0.8%)	2 (0.4%)	4 (0.6%)
	AMNESIA	0 .	1 (0.2%)	1 (0.1%)
	ANXIETY	13 (5.3%)	12 (2.5%)	25 (3.5%)
	APATHY	1 (0.4%)	0 .	1 (0.1%)
	CONCENTRATION IMPAIRED	1 (0.4%)	0 .	1 (0.1%)
	CONFUSION	0 .	3 (0.6%)	3 (0.4%)
	DEPRESSION	10 (4.1%)	21 (4.4%)	31 (4.3%)
	DEPRESSION AGGRAVATED	0 .	1 (0.2%)	1 (0.1%)
	INSOMNIA	8 (3.3%)	23 (4.8%)	31 (4.3%)
	NERVOUSNESS	5 (2.1%)	2 (0.4%)	7 (1.0%)
	SOMNOLENCE	4 (1.6%)	3 (0.6%)	7 (1.0%)
	SUICIDE ATTEMPT	0 .	1 (0.2%)	1 (0.1%)
RED BLOOD CELL	TOTAL	3 (1.2%)	16 (3.3%)	19 (2.6%)
	ANEMIA	2 (0.8%)	8 (1.7%)	10 (1.4%)
	ANEMIA HYPOCHROMIC	0 .	1 (0.2%)	1 (0.1%)
	ANEMIA MACROCYTIC	1 (0.4%)	0 .	1 (0.1%)
	ERYTHROCYTES ABNORMAL	0 .	1 (0.2%)	1 (0.1%)
	POLYCYTHEMIA	0 .	6 (1.3%)	6 (0.8%)
REPRODUCTIVE FEMALE	TOTAL	1 (0.4%)	5 (1.0%)	6 (0.8%)
	MENSTRUAL DISORDER	0 .	1 (0.2%)	1 (0.1%)
	PELVIC INFLAMMATION	1 (0.4%)	0 .	1 (0.1%)
	VAGINAL HEMORRHAGE	0 .	1 (0.2%)	1 (0.1%)
	VAGINITIS	0 .	3 (0.6%)	3 (0.4%)
REPRODUCTIVE MALE	TOTAL	15 (6.2%)	13 (2.7%)	28 (3.9%)
	BALANOPOSTHITIS	1 (0.4%)	0 .	1 (0.1%)
	IMPOTENCE	2 (0.8%)	6 (1.3%)	8 (1.1%)
	ORCHITIS	1 (0.4%)	0 .	1 (0.1%)
	PENIS DISORDER	1 (0.4%)	0 .	1 (0.1%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM/PREFERRED TERM
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3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
REPRODUCTIVE MALE	PROSTATIC DISORDER	11 (4.5%)	6 (1.3%)	17 (2.4%)
	TESTIS DISORDER	0 .	1 (0.2%)	1 (0.1%)
RESISTANCE MECHANISM	TOTAL	50 (20.6%)	111 (23.1%)	161 (22.3%)
	ABSCCESS	2 (0.8%)	4 (0.8%)	6 (0.8%)
	HERPES SIMPLEX	1 (0.4%)	3 (0.6%)	4 (0.6%)
	HERPES ZOSTER	2 (0.8%)	8 (1.7%)	10 (1.4%)
	INFECTION	6 (2.5%)	11 (2.3%)	17 (2.4%)
	INFECTION BACTERIAL	0 .	2 (0.4%)	2 (0.3%)
	INFECTION FUNGAL	4 (1.6%)	2 (0.4%)	6 (0.8%)
	INFECTION VIRAL	21 (8.6%)	39 (8.1%)	60 (8.3%)
	MONILIASIS	3 (1.2%)	6 (1.3%)	9 (1.2%)
	MONILIASIS GENITAL	0 .	1 (0.2%)	1 (0.1%)
	OTITIS MEDIA	3 (1.2%)	5 (1.0%)	8 (1.1%)
	SEPSIS	1 (0.4%)	2 (0.4%)	3 (0.4%)
	UPPER RESP TRACT INFECTION	20 (8.2%)	51 (10.6%)	71 (9.8%)
RESPIRATORY SYSTEM	TOTAL	174 (71.6%)	357 (74.4%)	531 (73.4%)
	APNEA	1 (0.4%)	1 (0.2%)	2 (0.3%)
	ASTHMA	2 (0.8%)	1 (0.2%)	3 (0.4%)
	BRONCHITIS	8 (3.3%)	14 (2.9%)	22 (3.0%)
	CHEST X-RAY ABNORMAL	0 .	3 (0.6%)	3 (0.4%)
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	155 (63.8%)	327 (68.1%)	482 (66.7%)
	COUGHING	13 (5.3%)	31 (6.5%)	44 (6.1%)
	DYSPNEA	8 (3.3%)	13 (2.7%)	21 (2.9%)
	EPISTAXIS	1 (0.4%)	3 (0.6%)	4 (0.6%)
	HEMOPTYSIS	3 (1.2%)	7 (1.5%)	10 (1.4%)
	HYPERVENTILATION	1 (0.4%)	0 .	1 (0.1%)
	HYPOXIA	1 (0.4%)	1 (0.2%)	2 (0.3%)
	LARYNGITIS	3 (1.2%)	2 (0.4%)	5 (0.7%)
	PHARYNGITIS	15 (6.2%)	42 (8.8%)	57 (7.9%)
	PLEURAL EFFUSION	1 (0.4%)	1 (0.2%)	2 (0.3%)
	PLEURAL PAIN	0 .	2 (0.4%)	2 (0.3%)
	PLEURISY	0 .	2 (0.4%)	2 (0.3%)
	PNEUMONIA	10 (4.1%)	14 (2.9%)	24 (3.3%)
	PNEUMONIA LOBAR	0 .	1 (0.2%)	1 (0.1%)
	RESPIRATORY DISORDER	10 (4.1%)	28 (5.8%)	38 (5.3%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM/PREFERRED TERM
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3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

SB 207499

TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
RESPIRATORY SYSTEM	RESPIRATORY INSUFFICIENCY	0	3 (0.6%)	3 (0.4%)
	RHINITIS	28 (11.5%)	44 (9.2%)	72 (10.0%)
	SINUSITIS	14 (5.8%)	16 (3.3%)	30 (4.1%)
	SPUTUM INCREASED	1 (0.4%)	6 (1.3%)	7 (1.0%)
	TRACHEITIS	1 (0.4%)	3 (0.6%)	4 (0.6%)
SKIN AND APPENDAGES	TOTAL	26 (10.7%)	47 (9.8%)	73 (10.1%)
	ALOPECIA	0	2 (0.4%)	2 (0.3%)
	ANGIOEDEMA	0	1 (0.2%)	1 (0.1%)
	BULLOUS ERUPTION	0	1 (0.2%)	1 (0.1%)
	DERMATITIS	2 (0.8%)	6 (1.3%)	8 (1.1%)
	DERMATITIS FUNGAL	1 (0.4%)	1 (0.2%)	2 (0.3%)
	DERMATITIS LICHENOID	0	2 (0.4%)	2 (0.3%)
	ECZEMA	4 (1.6%)	5 (1.0%)	9 (1.2%)
	FOLLICULITIS	0	2 (0.4%)	2 (0.3%)
	FURUNCULOSIS	1 (0.4%)	0	1 (0.1%)
	HYPERKERATOSIS	1 (0.4%)	1 (0.2%)	2 (0.3%)
	MELANOSIS	0	1 (0.2%)	1 (0.1%)
	NAIL DISORDER	1 (0.4%)	0	1 (0.1%)
	PHOTOSENSITIVITY	1 (0.4%)	0	1 (0.1%)
	ALLERGIC REACT			
	PRURITUS	4 (1.6%)	14 (2.9%)	18 (2.5%)
	PSORIASIS	0	1 (0.2%)	1 (0.1%)
	RASH	4 (1.6%)	5 (1.0%)	9 (1.2%)
	RASH ERYTHEMATOUS	1 (0.4%)	1 (0.2%)	2 (0.3%)
	RASH MACULO-PAPULAR	0	3 (0.6%)	3 (0.4%)
	RASH PUSTULAR	0	1 (0.2%)	1 (0.1%)
	ROSACEA	1 (0.4%)	0	1 (0.1%)
	SKIN DISORDER	4 (1.6%)	5 (1.0%)	9 (1.2%)
	SKIN DRY	3 (1.2%)	2 (0.4%)	5 (0.7%)
	SKIN HYPERTROPHY	2 (0.8%)	1 (0.2%)	3 (0.4%)
	SKIN ULCERATION	0	4 (0.8%)	4 (0.6%)
	URTICARIA	1 (0.4%)	7 (1.5%)	8 (1.1%)
	VERRUCA	1 (0.4%)	0	1 (0.1%)
SPECIAL SENSES	TOTAL	1 (0.4%)	2 (0.4%)	3 (0.4%)
OTHER	TASTE PERVERSION	1 (0.4%)	2 (0.4%)	3 (0.4%)
URINARY SYSTEM	TOTAL	35 (14.4%)	65 (13.5%)	100 (13.8%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM/PREFERRED TERM
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4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
URINARY SYSTEM	ALBUMINURIA	5 (2.1%)	12 (2.5%)	17 (2.4%)
	BLADDER CALCULUS	0 .	1 (0.2%)	1 (0.1%)
	CYSTITIS	2 (0.8%)	5 (1.0%)	7 (1.0%)
	DYSURIA	5 (2.1%)	3 (0.6%)	8 (1.1%)
	HEMATURIA	13 (5.3%)	13 (2.7%)	26 (3.6%)
	MICTURITION DISORDER	1 (0.4%)	1 (0.2%)	2 (0.3%)
	MICTURITION FREQUENCY	2 (0.8%)	3 (0.6%)	5 (0.7%)
	NOCTURIA	0 .	1 (0.2%)	1 (0.1%)
	PYELONEPHRITIS	0 .	2 (0.4%)	2 (0.3%)
	PYURIA	4 (1.6%)	12 (2.5%)	16 (2.2%)
	RENAL CALCULUS	1 (0.4%)	1 (0.2%)	2 (0.3%)
	RENAL CYST	0 .	1 (0.2%)	1 (0.1%)
	RENAL FAILURE ACUTE	0 .	2 (0.4%)	2 (0.3%)
	RENAL FUNCTION ABNORMAL	2 (0.8%)	1 (0.2%)	3 (0.4%)
	RENAL PAIN	0 .	3 (0.6%)	3 (0.4%)
	URINARY CASTS	1 (0.4%)	0 .	1 (0.1%)
	URINARY INCONTINENCE	0 .	2 (0.4%)	2 (0.3%)
	URINARY RETENTION	2 (0.8%)	4 (0.8%)	6 (0.8%)
	URINARY TRACT INFECTION	10 (4.1%)	22 (4.6%)	32 (4.4%)
	URINE ABNORMAL	0 .	1 (0.2%)	1 (0.1%)
VASCULAR EXTRACARDIAC	TOTAL	12 (4.9%)	20 (4.2%)	32 (4.4%)
	ARTERIOSCLEROSIS	0 .	1 (0.2%)	1 (0.1%)
	ARTERITIS	1 (0.4%)	0 .	1 (0.1%)
	CEREBROVASCULAR DISORDER	1 (0.4%)	4 (0.8%)	5 (0.7%)
	CLAUDICATION INTERMITTENT	2 (0.8%)	1 (0.2%)	3 (0.4%)
	CRAMPS LEGS	2 (0.8%)	2 (0.4%)	4 (0.6%)
	HEMORRHAGE NOS	1 (0.4%)	0 .	1 (0.1%)
	PERIPHERAL ISCHEMIA	2 (0.8%)	1 (0.2%)	3 (0.4%)
	PHLEBITIS	0 .	1 (0.2%)	1 (0.1%)
	PHLEBITIS SUPERFICIAL	0 .	1 (0.2%)	1 (0.1%)
	THROMBOPHLEBITIS DEEP	2 (0.8%)	0 .	2 (0.3%)
	THROMBOPHLEBITIS LEG	0 .	1 (0.2%)	1 (0.1%)
	THROMBOPHLEBITIS RETINAL VEIN	0 .	1 (0.2%)	1 (0.1%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM/PREFERRED TERM
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4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 15.2B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
VASCULAR EXTRACARDIAC	THROMBOSIS ARTERIAL LEG	0 .	1 (0.2%)	1 (0.1%)
	THROMBOSIS RETINAL ARTERY	0 .	2 (0.4%)	2 (0.3%)
	VASCULAR DISORDER	1 (0.4%)	3 (0.6%)	4 (0.6%)
	VEIN DISORDER	1 (0.4%)	1 (0.2%)	2 (0.3%)
	VEIN VARICOSE	0 .	3 (0.6%)	3 (0.4%)
	TOTAL	17 (7.0%)	21 (4.4%)	38 (5.3%)
VISION	BLEPHARITIS	2 (0.8%)	1 (0.2%)	3 (0.4%)
	CATARACT	6 (2.5%)	6 (1.3%)	12 (1.7%)
	CONJUNCTIVAL HEMORRHAGE	0 .	1 (0.2%)	1 (0.1%)
	CONJUNCTIVITIS	7 (2.9%)	8 (1.7%)	15 (2.1%)
	CORNEAL ULCERATION	0 .	1 (0.2%)	1 (0.1%)
	EYE ABNORMALITY	2 (0.8%)	2 (0.4%)	4 (0.6%)
	GLAUCOMA	0 .	1 (0.2%)	1 (0.1%)
	MACULA LUTEA DEGENERATION	1 (0.4%)	0 .	1 (0.1%)
	RETINAL DETACHMENT	1 (0.4%)	0 .	1 (0.1%)
	RETINAL DISORDER	2 (0.8%)	0 .	2 (0.3%)
	UVEITIS	0 .	1 (0.2%)	1 (0.1%)
	VISION ABNORMAL	2 (0.8%)	1 (0.2%)	3 (0.4%)
	VISUAL FIELD DEFECT	0 .	1 (0.2%)	1 (0.1%)
	XEROPHTHALMIA	2 (0.8%)	0 .	2 (0.3%)
	TOTAL	13 (5.3%)	23 (4.8%)	36 (5.0%)
WHITE CELL AND RETICULOENDOTHELIAL SYSTE	EOSINOPHILIA	0 .	2 (0.4%)	2 (0.3%)
	GRANULOCYTOPENIA	0 .	2 (0.4%)	2 (0.3%)
	LEUKOCYTOSIS	6 (2.5%)	17 (3.5%)	23 (3.2%)
	LEUKOPENIA	1 (0.4%)	2 (0.4%)	3 (0.4%)
	LYMPHADENOPATHY	3 (1.2%)	2 (0.4%)	5 (0.7%)
	LYMPHADENOPATHY CERVICAL	0 .	1 (0.2%)	1 (0.1%)
	LYMPHANGITIS	1 (0.4%)	0 .	1 (0.1%)
	LYMPHEDEMA	1 (0.4%)	0 .	1 (0.1%)
	LYMPHOPENIA	1 (0.4%)	1 (0.2%)	2 (0.3%)
	TOTAL	13 (5.3%)	23 (4.8%)	36 (5.0%)
	EOSINOPHILIA	0 .	2 (0.4%)	2 (0.3%)
	GRANULOCYTOPENIA	0 .	2 (0.4%)	2 (0.3%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM/PREFERRED TERM
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3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: PLACEBO (N= 243)

WHO BODY SYSTEM	WHO PREFERRED TERM	----- Relationship -----		-----	
		Not-Related	Related	Total	
TOTAL	TOTAL	140 (57.6%)	89 (36.6%)	229 (94.2%)	
APPLICATION SITE	TOTAL	3 (1.2%)	0 .	3 (1.2%)	
	OTITIS EXTERNA	3 (1.2%)	0 .	3 (1.2%)	
AUTONOMIC NERVOUS SYSTEM	TOTAL	3 (1.2%)	2 (0.8%)	5 (2.1%)	
	MOUTH DRY	1 (0.4%)	0 .	1 (0.4%)	
	SWEATING INCREASED	2 (0.8%)	2 (0.8%)	4 (1.6%)	
BODY AS A WHOLE GENERAL	TOTAL	69 (28.4%)	5 (2.1%)	74 (30.5%)	
	ALCOHOL INTOLERANCE	1 (0.4%)	0 .	1 (0.4%)	
	ALLERGIC REACTION	2 (0.8%)	0 .	2 (0.8%)	
	ASTHENIA	8 (3.3%)	0 .	8 (3.3%)	
	CELLULITIS	1 (0.4%)	0 .	1 (0.4%)	
	CHEST PAIN	14 (5.8%)	1 (0.4%)	15 (6.2%)	
	CHEST PAIN PRECORDIAL	4 (1.6%)	0 .	4 (1.6%)	
	CHEST PAIN SUBSTERNAL	1 (0.4%)	0 .	1 (0.4%)	
	EDEMA DEPENDENT	3 (1.2%)	0 .	3 (1.2%)	
	EDEMA LEGS	5 (2.1%)	0 .	5 (2.1%)	
	FATIGUE	5 (2.1%)	3 (1.2%)	8 (3.3%)	
	FEVER	11 (4.5%)	0 .	11 (4.5%)	
	HOT FLUSHES	1 (0.4%)	0 .	1 (0.4%)	
	INFLUENZA-LIKE SYMPTOMS	1 (0.4%)	0 .	1 (0.4%)	
	INJURY	26 (10.7%)	0 .	26 (10.7%)	
	MALAISE	9 (3.7%)	1 (0.4%)	10 (4.1%)	
	PAIN	9 (3.7%)	0 .	9 (3.7%)	
	RIGORS	1 (0.4%)	0 .	1 (0.4%)	
CARDIOVASCULAR GENERAL	TOTAL	22 (9.1%)	2 (0.8%)	24 (9.9%)	
	ANEURYSM	1 (0.4%)	0 .	1 (0.4%)	
	CARDIAC FAILURE	2 (0.8%)	0 .	2 (0.8%)	
	CARDIOMEGALY	1 (0.4%)	0 .	1 (0.4%)	
	ECG ABNORMAL	1 (0.4%)	0 .	1 (0.4%)	
	ECG ABNORMAL SPECIFIC	1 (0.4%)	0 .	1 (0.4%)	
	HEART VALVE DISORDERS	1 (0.4%)	0 .	1 (0.4%)	
	HYPERTENSION	9 (3.7%)	1 (0.4%)	10 (4.1%)	

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM, PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED
3. LIKELIEST RELATIONSHIP IS USED FOR EACH ADVERSE EVENT FOR EACH PATIENT
4. NOT RELATED=UNLIKELY OR NOT-RELATED TO TREATMENT, RELATED=SUSPECTED OR PROBABLY RELATED TO TREATMENT

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: PLACEBO (N= 243)

WHO BODY SYSTEM	WHO PREFERRED TERM	Relationship		Total
		Not-Related	Related	
CARDIOVASCULAR GENERAL	HYPERTENSION	3 (1.2%)	0 .	3 (1.2%)
	AGGRAVATED			
	HYPOTENSION	1 (0.4%)	0 .	1 (0.4%)
	HYPOTENSION POSTURAL	0 .	1 (0.4%)	1 (0.4%)
	SYNCOPE	4 (1.6%)	0 .	4 (1.6%)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	TOTAL	40 (16.5%)	18 (7.4%)	58 (23.9%)
	ATAXIA	1 (0.4%)	0 .	1 (0.4%)
	DIZZINESS	3 (1.2%)	6 (2.5%)	9 (3.7%)
	DYSPHONIA	1 (0.4%)	0 .	1 (0.4%)
	EXTRAPYRAMIDAL DISORDER	1 (0.4%)	0 .	1 (0.4%)
	HEADACHE	19 (7.8%)	13 (5.3%)	32 (13.2%)
	HYPERTONIA	1 (0.4%)	0 .	1 (0.4%)
	HYPESTHESIA	1 (0.4%)	0 .	1 (0.4%)
	MIGRAINE	2 (0.8%)	0 .	2 (0.8%)
	MUSCLE CONTRACTIONS INVOLUNTARY	1 (0.4%)	0 .	1 (0.4%)
	NEURALGIA	7 (2.9%)	0 .	7 (2.9%)
	PARESIS	2 (0.8%)	0 .	2 (0.8%)
	PARESTHESIA	2 (0.8%)	0 .	2 (0.8%)
	TREMOR	1 (0.4%)	2 (0.8%)	3 (1.2%)
	TRIGEMINAL NEURALGIA	1 (0.4%)	0 .	1 (0.4%)
	VERTIGO	5 (2.1%)	0 .	5 (2.1%)
ENDOCRINE	TOTAL	4 (1.6%)	0 .	4 (1.6%)
	GOITRE	1 (0.4%)	0 .	1 (0.4%)
	HYPERTHYROIDISM	1 (0.4%)	0 .	1 (0.4%)
	MASTITIS MALE	1 (0.4%)	0 .	1 (0.4%)
	SIALOADENITIS	1 (0.4%)	0 .	1 (0.4%)
	THYROIDITIS	1 (0.4%)	0 .	1 (0.4%)
GASTROINTESTINAL SYSTEM	TOTAL	60 (24.7%)	74 (30.5%)	134 (55.1%)
	ABDOMINAL PAIN	15 (6.2%)	35 (14.4%)	50 (20.6%)
	ANOREXIA	4 (1.6%)	3 (1.2%)	7 (2.9%)
	APPETITE INCREASED	1 (0.4%)	0 .	1 (0.4%)
	CONSTIPATION	5 (2.1%)	0 .	5 (2.1%)

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TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, BODY SYSTEM,
PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: PLACEBO (N= 243)

WHO BODY SYSTEM	WHO PREFERRED TERM	Relationship		Total
		Not-Related	Related	
GASTROINTESTINAL SYSTEM	DIARRHEA	21 (8.6%)	23 (9.5%)	44 (18.1%)
	DUODENITIS	1 (0.4%)	0 .	1 (0.4%)
	DYSPEPSIA	13 (5.3%)	17 (7.0%)	30 (12.3%)
	ENTERITIS	2 (0.8%)	0 .	2 (0.8%)
	ESOPHAGITIS	2 (0.8%)	1 (0.4%)	3 (1.2%)
	ESOPHAGOSPASM	1 (0.4%)	0 .	1 (0.4%)
	FLATULENCE	5 (2.1%)	0 .	5 (2.1%)
	GASTRITIS	4 (1.6%)	2 (0.8%)	6 (2.5%)
	GASTROENTERITIS	11 (4.5%)	0 .	11 (4.5%)
	GASTROESOPHAGEAL REFLUX	2 (0.8%)	1 (0.4%)	3 (1.2%)
	GASTROINTESTINAL DISORDER NOS	4 (1.6%)	1 (0.4%)	5 (2.1%)
	GI HEMORRHAGE	2 (0.8%)	1 (0.4%)	3 (1.2%)
	HEMORRHAGE RECTUM	1 (0.4%)	0 .	1 (0.4%)
	HEMORRHOIDS	2 (0.8%)	0 .	2 (0.8%)
	INTESTINAL OBSTRUCTION	1 (0.4%)	0 .	1 (0.4%)
	IRRITABLE BOWEL SYNDROME	1 (0.4%)	0 .	1 (0.4%)
	MELENA	3 (1.2%)	2 (0.8%)	5 (2.1%)
	NAUSEA	12 (4.9%)	22 (9.1%)	34 (14.0%)
	PANCREATITIS	0 .	1 (0.4%)	1 (0.4%)
	PERIODONTITIS	5 (2.1%)	0 .	5 (2.1%)
	PROCTITIS	1 (0.4%)	0 .	1 (0.4%)
	STOMATITIS	1 (0.4%)	0 .	1 (0.4%)
	TOOTH ACHE	2 (0.8%)	0 .	2 (0.8%)
	TOOTH CARIES	2 (0.8%)	0 .	2 (0.8%)
	TOOTH DISORDER	1 (0.4%)	0 .	1 (0.4%)
	VOMITING	3 (1.2%)	12 (4.9%)	15 (6.2%)
HEARING AND VESTIBULAR	TOTAL	8 (3.3%)	0 .	8 (3.3%)
	DEAFNESS	1 (0.4%)	0 .	1 (0.4%)
	EAR DISORDER NOS	3 (1.2%)	0 .	3 (1.2%)
	EARACHE	1 (0.4%)	0 .	1 (0.4%)
	TINNITUS	2 (0.8%)	0 .	2 (0.8%)
	VESTIBULAR DISORDER	1 (0.4%)	0 .	1 (0.4%)

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TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: PLACEBO (N= 243)

WHO BODY SYSTEM	WHO PREFERRED TERM	Relationship		Total
		Not-Related	Related	
HEART RATE AND RHYTHM	TOTAL	25 (10.3%)	6 (2.5%)	31 (12.8%)
	ARRHYTHMIA	4 (1.6%)	0 .	4 (1.6%)
	ARRHYTHMIA ATRIAL	1 (0.4%)	0 .	1 (0.4%)
	BRADYCARDIA	5 (2.1%)	2 (0.8%)	7 (2.9%)
	BUNDLE BRANCH BLOCK	2 (0.8%)	0 .	2 (0.8%)
	EXTRASYSTOLES	3 (1.2%)	1 (0.4%)	4 (1.6%)
	EXTRASYSTOLES SUPRAVENTRICULAR	3 (1.2%)	2 (0.8%)	5 (2.1%)
	FIBRILLATION ATRIAL	2 (0.8%)	1 (0.4%)	3 (1.2%)
	QT INCREASED	1 (0.4%)	0 .	1 (0.4%)
	TACHYCARDIA	9 (3.7%)	1 (0.4%)	10 (4.1%)
LIVER AND BILIARY SYSTEM	TOTAL	10 (4.1%)	3 (1.2%)	13 (5.3%)
	BILIRUBINEMIA	0 .	1 (0.4%)	1 (0.4%)
	CHOLELITHIASIS	2 (0.8%)	0 .	2 (0.8%)
	GAMMA-GT INCREASED	5 (2.1%)	2 (0.8%)	7 (2.9%)
	HEPATIC CIRRHOSIS	1 (0.4%)	0 .	1 (0.4%)
	HEPATIC ENZYMES INCREASED	2 (0.8%)	1 (0.4%)	3 (1.2%)
	HEPATITIS INFECTIOUS	1 (0.4%)	0 .	1 (0.4%)
	SGPT INCREASED	0 .	1 (0.4%)	1 (0.4%)
METABOLIC AND NUTRITIONAL	TOTAL	31 (12.8%)	5 (2.1%)	36 (14.8%)
	DIABETES MELLITUS	2 (0.8%)	0 .	2 (0.8%)
	GLYCOSURIA	4 (1.6%)	0 .	4 (1.6%)
	GOUT	5 (2.1%)	0 .	5 (2.1%)
	HYPERCHOLESTEROLEMIA	4 (1.6%)	0 .	4 (1.6%)
	HYPERGLYCEMIA	7 (2.9%)	1 (0.4%)	8 (3.3%)
	HYPERKALEMIA	0 .	1 (0.4%)	1 (0.4%)
	HYPERNATREMIA	0 .	1 (0.4%)	1 (0.4%)
	HYPERTRIGLYCERIDEMIA	1 (0.4%)	0 .	1 (0.4%)
	HYPERURICEMIA	3 (1.2%)	0 .	3 (1.2%)
	HYPOCHLOREMIA	1 (0.4%)	0 .	1 (0.4%)
	HYPOGLYCEMIA	1 (0.4%)	0 .	1 (0.4%)
	HYPOKALEMIA	1 (0.4%)	1 (0.4%)	2 (0.8%)
	HYPONATREMIA	2 (0.8%)	0 .	2 (0.8%)
	OBESITY	1 (0.4%)	0 .	1 (0.4%)

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PROTOCOL 040

PRIOR TREATMENT: PLACEBO (N= 243)

WHO BODY SYSTEM	WHO PREFERRED TERM	Relationship		Total
		Not-Related	Related	
METABOLIC AND NUTRITIONAL	WEIGHT DECREASE	7 (2.9%)	2 (0.8%)	9 (3.7%)
	WEIGHT INCREASE	1 (0.4%)	0 .	1 (0.4%)
MUSCULOSKELETAL SYSTEM	TOTAL	60 (24.7%)	0 .	60 (24.7%)
	ARTHRALGIA	20 (8.2%)	0 .	20 (8.2%)
	ARTHRITIS	7 (2.9%)	0 .	7 (2.9%)
	ARTHRITIS AGGRAVATED	2 (0.8%)	0 .	2 (0.8%)
	ARTHROPATHY	2 (0.8%)	0 .	2 (0.8%)
	ARTHROSIS	2 (0.8%)	0 .	2 (0.8%)
	BACK PAIN	23 (9.5%)	0 .	23 (9.5%)
	MYALGIA	13 (5.3%)	0 .	13 (5.3%)
	MYOSITIS	1 (0.4%)	0 .	1 (0.4%)
	OSTEONECROSIS	1 (0.4%)	0 .	1 (0.4%)
	OSTEOPOROSIS	1 (0.4%)	0 .	1 (0.4%)
	SKELETAL PAIN	2 (0.8%)	0 .	2 (0.8%)
	TENDON DISORDER	1 (0.4%)	0 .	1 (0.4%)
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	TOTAL	9 (3.7%)	0 .	9 (3.7%)
	ANGINA PECTORIS	7 (2.9%)	0 .	7 (2.9%)
	AORTIC STENOSIS	1 (0.4%)	0 .	1 (0.4%)
	MYOCARDIAL INFARCTION	1 (0.4%)	0 .	1 (0.4%)
NEOPLASM	TOTAL	23 (9.5%)	0 .	23 (9.5%)
	ADENOCARCINOMA NOS	1 (0.4%)	0 .	1 (0.4%)
	BASAL CELL CARCINOMA	1 (0.4%)	0 .	1 (0.4%)
	BLADDER CARCINOMA	2 (0.8%)	0 .	2 (0.8%)
	CARCINOMA	3 (1.2%)	0 .	3 (1.2%)
	COLON CARCINOMA	1 (0.4%)	0 .	1 (0.4%)
	GASTRIC CARCINOMA	1 (0.4%)	0 .	1 (0.4%)
	LIPOMA	2 (0.8%)	0 .	2 (0.8%)
	LYMPHOMA MALIGNANT	1 (0.4%)	0 .	1 (0.4%)
	NEOPLASM MALIGNANT	1 (0.4%)	0 .	1 (0.4%)
	NEOPLASM NOS	10 (4.1%)	0 .	10 (4.1%)
	PULMONARY CARCINOMA	1 (0.4%)	0 .	1 (0.4%)

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INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, BODY SYSTEM,
PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: PLACEBO (N= 243)

WHO BODY SYSTEM	WHO PREFERRED TERM	Relationship		Total
		Not-Related	Related	
PLATELET BLEEDING AND CLOTTING	TOTAL	1 (0.4%)	0 .	1 (0.4%)
	PURPURA	1 (0.4%)	0 .	1 (0.4%)
PSYCHIATRIC	TOTAL	31 (12.8%)	4 (1.6%)	35 (14.4%)
	AGITATION	2 (0.8%)	0 .	2 (0.8%)
	ANXIETY	12 (4.9%)	1 (0.4%)	13 (5.3%)
	APATHY	1 (0.4%)	0 .	1 (0.4%)
	CONCENTRATION IMPAIRED	1 (0.4%)	0 .	1 (0.4%)
	DEPRESSION	10 (4.1%)	0 .	10 (4.1%)
	INSOMNIA	7 (2.9%)	1 (0.4%)	8 (3.3%)
	NERVOUSNESS	3 (1.2%)	2 (0.8%)	5 (2.1%)
RED BLOOD CELL	SOMNOLENCE	4 (1.6%)	0 .	4 (1.6%)
	TOTAL	3 (1.2%)	0 .	3 (1.2%)
	ANEMIA	2 (0.8%)	0 .	2 (0.8%)
	ANEMIA MACROCYTIC	1 (0.4%)	0 .	1 (0.4%)
REPRODUCTIVE FEMALE	TOTAL	1 (0.4%)	0 .	1 (0.4%)
	PELVIC INFLAMMATION	1 (0.4%)	0 .	1 (0.4%)
REPRODUCTIVE MALE	TOTAL	15 (6.2%)	0 .	15 (6.2%)
	BALANOPOSTHITIS	1 (0.4%)	0 .	1 (0.4%)
	IMPOTENCE	2 (0.8%)	0 .	2 (0.8%)
	ORCHITIS	1 (0.4%)	0 .	1 (0.4%)
	PENIS DISORDER	1 (0.4%)	0 .	1 (0.4%)
	PROSTATIC DISORDER	11 (4.5%)	0 .	11 (4.5%)
RESISTANCE MECHANISM	TOTAL	49 (20.2%)	1 (0.4%)	50 (20.6%)
	ABSCCESS	2 (0.8%)	0 .	2 (0.8%)
	HERPES SIMPLEX	1 (0.4%)	0 .	1 (0.4%)
	HERPES ZOSTER	2 (0.8%)	0 .	2 (0.8%)
	INFECTION	6 (2.5%)	0 .	6 (2.5%)
	INFECTION FUNGAL	4 (1.6%)	0 .	4 (1.6%)
	INFECTION VIRAL	20 (8.2%)	1 (0.4%)	21 (8.6%)
	MONILIASIS	3 (1.2%)	0 .	3 (1.2%)
	OTITIS MEDIA	3 (1.2%)	0 .	3 (1.2%)
	SEPSIS	1 (0.4%)	0 .	1 (0.4%)

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INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, BODY SYSTEM,
PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: PLACEBO (N= 243)

WHO BODY SYSTEM	WHO PREFERRED TERM	Relationship		Total
		Not-Related	Related	
RESISTANCE MECHANISM	UPPER RESP TRACT INFECTION	19 (7.8%)	1 (0.4%)	20 (8.2%)
RESPIRATORY SYSTEM	TOTAL	168 (69.1%)	6 (2.5%)	174 (71.6%)
	APNEA	1 (0.4%)	0 .	1 (0.4%)
	ASTHMA	2 (0.8%)	0 .	2 (0.8%)
	BRONCHITIS	8 (3.3%)	0 .	8 (3.3%)
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	150 (61.7%)	5 (2.1%)	155 (63.8%)
	COUGHING	12 (4.9%)	1 (0.4%)	13 (5.3%)
	DYSPNEA	8 (3.3%)	0 .	8 (3.3%)
	EPISTAXIS	1 (0.4%)	0 .	1 (0.4%)
	HEMOPTYSIS	3 (1.2%)	0 .	3 (1.2%)
	HYPERVENTILATION	1 (0.4%)	0 .	1 (0.4%)
	HYPOXIA	1 (0.4%)	0 .	1 (0.4%)
	LARYNGITIS	3 (1.2%)	0 .	3 (1.2%)
	PHARYNGITIS	15 (6.2%)	0 .	15 (6.2%)
	PLEURAL EFFUSION	1 (0.4%)	0 .	1 (0.4%)
	PNEUMONIA	10 (4.1%)	0 .	10 (4.1%)
	RESPIRATORY DISORDER	10 (4.1%)	0 .	10 (4.1%)
	RHINITIS	28 (11.5%)	0 .	28 (11.5%)
	SINUSITIS	14 (5.8%)	0 .	14 (5.8%)
	SPUTUM INCREASED	1 (0.4%)	0 .	1 (0.4%)
	TRACHEITIS	1 (0.4%)	0 .	1 (0.4%)
SKIN AND APPENDAGES	TOTAL	25 (10.3%)	1 (0.4%)	26 (10.7%)
	DERMATITIS	2 (0.8%)	0 .	2 (0.8%)
	DERMATITIS FUNGAL	1 (0.4%)	0 .	1 (0.4%)
	ECZEMA	4 (1.6%)	0 .	4 (1.6%)
	FURUNCULOSIS	1 (0.4%)	0 .	1 (0.4%)
	HYPERKERATOSIS	1 (0.4%)	0 .	1 (0.4%)
	NAIL DISORDER	1 (0.4%)	0 .	1 (0.4%)
	PHOTOSENSITIVITY	1 (0.4%)	0 .	1 (0.4%)
	ALLERGIC REACT			
	PRURITUS	3 (1.2%)	1 (0.4%)	4 (1.6%)
	RASH	4 (1.6%)	0 .	4 (1.6%)
	RASH ERYTHEMATOUS	1 (0.4%)	0 .	1 (0.4%)
	ROSACEA	1 (0.4%)	0 .	1 (0.4%)
	SKIN DISORDER	4 (1.6%)	0 .	4 (1.6%)
	SKIN DRY	3 (1.2%)	0 .	3 (1.2%)

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PROTOCOL 040

PRIOR TREATMENT: PLACEBO (N= 243)

WHO BODY SYSTEM	WHO PREFERRED TERM	Relationship		Total
		Not-Related	Related	
SKIN AND APPENDAGES	SKIN HYPERTROPHY	2 (0.8%)	0 .	2 (0.8%)
	URTICARIA	1 (0.4%)	0 .	1 (0.4%)
	VERRUCA	1 (0.4%)	0 .	1 (0.4%)
SPECIAL SENSES OTHER	TOTAL	0 .	1 (0.4%)	1 (0.4%)
	TASTE PERVERSION	0 .	1 (0.4%)	1 (0.4%)
URINARY SYSTEM	TOTAL	34 (14.0%)	1 (0.4%)	35 (14.4%)
	ALBUMINURIA	5 (2.1%)	0 .	5 (2.1%)
	CYSTITIS	2 (0.8%)	0 .	2 (0.8%)
	DYSURIA	5 (2.1%)	0 .	5 (2.1%)
	HEMATURIA	12 (4.9%)	1 (0.4%)	13 (5.3%)
	MICTURITION DISORDER	1 (0.4%)	0 .	1 (0.4%)
	MICTURITION FREQUENCY	2 (0.8%)	0 .	2 (0.8%)
	PYURIA	4 (1.6%)	0 .	4 (1.6%)
	RENAL CALCULUS	1 (0.4%)	0 .	1 (0.4%)
	RENAL FUNCTION ABNORMAL	2 (0.8%)	0 .	2 (0.8%)
	URINARY CASTS	1 (0.4%)	0 .	1 (0.4%)
	URINARY RETENTION	2 (0.8%)	0 .	2 (0.8%)
	URINARY TRACT INFECTION	10 (4.1%)	0 .	10 (4.1%)
VASCULAR EXTRACARDIAC	TOTAL	12 (4.9%)	0 .	12 (4.9%)
	ARTERITIS	1 (0.4%)	0 .	1 (0.4%)
	CEREBROVASCULAR DISORDER	1 (0.4%)	0 .	1 (0.4%)
	CLAUDICATION INTERMITTENT	2 (0.8%)	0 .	2 (0.8%)
	CRAMPS LEGS	2 (0.8%)	0 .	2 (0.8%)
	HEMORRHAGE NOS	1 (0.4%)	0 .	1 (0.4%)
	PERIPHERAL ISCHEMIA	2 (0.8%)	0 .	2 (0.8%)
	THROMBOPHLEBITIS DEEP	2 (0.8%)	0 .	2 (0.8%)
	VASCULAR DISORDER	1 (0.4%)	0 .	1 (0.4%)
	VEIN DISORDER	1 (0.4%)	0 .	1 (0.4%)
VISION	TOTAL	17 (7.0%)	0 .	17 (7.0%)
	BLEPHARITIS	2 (0.8%)	0 .	2 (0.8%)

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INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, BODY SYSTEM,
PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: PLACEBO (N= 243)

WHO BODY SYSTEM	WHO PREFERRED TERM	Relationship		Total
		Not-Related	Related	
VISION	CATARACT	6 (2.5%)	0 .	6 (2.5%)
	CONJUNCTIVITIS	7 (2.9%)	0 .	7 (2.9%)
	EYE ABNORMALITY	2 (0.8%)	0 .	2 (0.8%)
	MACULA LUTEA DEGENERATION	1 (0.4%)	0 .	1 (0.4%)
	RETINAL DETACHMENT	1 (0.4%)	0 .	1 (0.4%)
	RETINAL DISORDER	2 (0.8%)	0 .	2 (0.8%)
	VISION ABNORMAL	2 (0.8%)	0 .	2 (0.8%)
	XEROPHTHALMIA	2 (0.8%)	0 .	2 (0.8%)
WHITE CELL AND RETICULOENDOTHELIAL SYSTE	TOTAL	13 (5.3%)	0 .	13 (5.3%)
	LEUKOCYTOSIS	6 (2.5%)	0 .	6 (2.5%)
	LEUKOPENIA	1 (0.4%)	0 .	1 (0.4%)
	LYMPHADENOPATHY	3 (1.2%)	0 .	3 (1.2%)
	LYMPHANGITIS	1 (0.4%)	0 .	1 (0.4%)
	LYMPHEDEMA	1 (0.4%)	0 .	1 (0.4%)
	LYMPHOPENIA	1 (0.4%)	0 .	1 (0.4%)

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TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, BODY SYSTEM,
PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499 (N= 480)

WHO BODY SYSTEM	WHO PREFERRED TERM	----- Relationship -----		-----	
		Not-Related	Related	Total	
TOTAL	TOTAL	342 (71.3%)	104 (21.7%)	446 (92.9%)	
APPLICATION SITE	TOTAL	5 (1.0%)	0 .	5 (1.0%)	
	INJECTION SITE	1 (0.2%)	0 .	1 (0.2%)	
	INFLAMMATION				
	OTITIS EXTERNA	5 (1.0%)	0 .	5 (1.0%)	
	TYMPANIC MEMBRANE PERFORATION	1 (0.2%)	0 .	1 (0.2%)	
AUTONOMIC NERVOUS SYSTEM	TOTAL	2 (0.4%)	0 .	2 (0.4%)	
	MOUTH DRY	2 (0.4%)	0 .	2 (0.4%)	
BODY AS A WHOLE GENERAL	TOTAL	126 (26.3%)	4 (0.8%)	130 (27.1%)	
	ALLERGIC REACTION	2 (0.4%)	0 .	2 (0.4%)	
	ASTHENIA	13 (2.7%)	2 (0.4%)	15 (3.1%)	
	CELLULITIS	4 (0.8%)	0 .	4 (0.8%)	
	CHEST PAIN	26 (5.4%)	0 .	26 (5.4%)	
	CHEST PAIN PRECORDIAL	2 (0.4%)	0 .	2 (0.4%)	
	CHEST PAIN SUBSTERNAL	1 (0.2%)	0 .	1 (0.2%)	
	DRUG LEVEL INCREASED	1 (0.2%)	0 .	1 (0.2%)	
	EDEMA	1 (0.2%)	0 .	1 (0.2%)	
	EDEMA DEPENDENT	4 (0.8%)	0 .	4 (0.8%)	
	EDEMA LEGS	5 (1.0%)	0 .	5 (1.0%)	
	FACE EDEMA	0 .	1 (0.2%)	1 (0.2%)	
	FATIGUE	8 (1.7%)	1 (0.2%)	9 (1.9%)	
	FEVER	8 (1.7%)	0 .	8 (1.7%)	
	INFLUENZA-LIKE SYMPTOMS	3 (0.6%)	0 .	3 (0.6%)	
	INJURY	62 (12.9%)	0 .	62 (12.9%)	
	MALAISE	5 (1.0%)	1 (0.2%)	6 (1.3%)	
	PAIN	22 (4.6%)	0 .	22 (4.6%)	
	RIGORS	1 (0.2%)	0 .	1 (0.2%)	
	THERAPEUTIC RESPONSE INCREASED	3 (0.6%)	0 .	3 (0.6%)	
CARDIOVASCULAR GENERAL	TOTAL	54 (11.3%)	3 (0.6%)	57 (11.9%)	
	ANEURYSM	2 (0.4%)	0 .	2 (0.4%)	

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM, PREFERRED TERM AND RELATIONSHIP
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4. NOT RELATED=UNLIKELY OR NOT-RELATED TO TREATMENT, RELATED=SUSPECTED OR PROBABLY RELATED TO TREATMENT

SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, BODY SYSTEM,
PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499 (N= 480)

WHO BODY SYSTEM	WHO PREFERRED TERM	Relationship		Total
		Not-Related	Related	
CARDIOVASCULAR GENERAL	CARDIAC FAILURE	3 (0.6%)	0 .	3 (0.6%)
	CARDIOMEGALY	2 (0.4%)	0 .	2 (0.4%)
	COR PULMONALE	1 (0.2%)	0 .	1 (0.2%)
	CYANOSIS	1 (0.2%)	0 .	1 (0.2%)
	ECG ABNORMAL	2 (0.4%)	0 .	2 (0.4%)
	ECG ABNORMAL SPECIFIC	2 (0.4%)	0 .	2 (0.4%)
	HYPERTENSION	31 (6.5%)	1 (0.2%)	32 (6.7%)
	HYPERTENSION AGGRAVATED	5 (1.0%)	0 .	5 (1.0%)
	HYPERTENSION PULMONARY	1 (0.2%)	0 .	1 (0.2%)
	HYPOTENSION	3 (0.6%)	2 (0.4%)	5 (1.0%)
	HYPOTENSION POSTURAL	4 (0.8%)	0 .	4 (0.8%)
	SYNCOPE	8 (1.7%)	0 .	8 (1.7%)
	TOTAL	84 (17.5%)	11 (2.3%)	95 (19.8%)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	COMA	1 (0.2%)	0 .	1 (0.2%)
	CONVULSIONS	2 (0.4%)	0 .	2 (0.4%)
	DIZZINESS	21 (4.4%)	4 (0.8%)	25 (5.2%)
	DYSPHONIA	4 (0.8%)	0 .	4 (0.8%)
	EXTRAPYRAMIDAL DISORDER	1 (0.2%)	0 .	1 (0.2%)
	HEADACHE	41 (8.5%)	6 (1.3%)	47 (9.8%)
	HYPERTONIA	3 (0.6%)	0 .	3 (0.6%)
	MIGRAINE	2 (0.4%)	0 .	2 (0.4%)
	MUSCLE CONTRACTIONS INVOLUNTARY	2 (0.4%)	0 .	2 (0.4%)
	NERVE ROOT LESION	1 (0.2%)	0 .	1 (0.2%)
	NEURALGIA	11 (2.3%)	0 .	11 (2.3%)
	NEUROPATHY	1 (0.2%)	0 .	1 (0.2%)
	NEUROPATHY PERIPHERAL	2 (0.4%)	0 .	2 (0.4%)
	PARESIS	1 (0.2%)	0 .	1 (0.2%)
	PARESTHESIA	2 (0.4%)	0 .	2 (0.4%)
	PARKINSONISM	1 (0.2%)	0 .	1 (0.2%)
	AGGRAVATED TREMOR	3 (0.6%)	0 .	3 (0.6%)
	VERTIGO	12 (2.5%)	1 (0.2%)	13 (2.7%)
	WITHDRAWAL HEADACHE	1 (0.2%)	0 .	1 (0.2%)

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SB 207499

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INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, BODY SYSTEM,
PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499 (N= 480)

WHO BODY SYSTEM	WHO PREFERRED TERM	Relationship		Total
		Not-Related	Related	
COLLAGEN	TOTAL	3 (0.6%)	0 .	3 (0.6%)
	ARTHRITIS RHEUMATOID	2 (0.4%)	0 .	2 (0.4%)
	ARTHRITIS RHEUMATOID AGGRAVATED	1 (0.2%)	0 .	1 (0.2%)
ENDOCRINE	TOTAL	9 (1.9%)	0 .	9 (1.9%)
	GOITRE	1 (0.2%)	0 .	1 (0.2%)
	HYPERTHYROIDISM	6 (1.3%)	0 .	6 (1.3%)
	HYPOTHYROIDISM	3 (0.6%)	0 .	3 (0.6%)
FETAL	TOTAL	1 (0.2%)	0 .	1 (0.2%)
	SPINE MALFORMATION	1 (0.2%)	0 .	1 (0.2%)
GASTROINTESTINAL SYSTEM	TOTAL	126 (26.3%)	70 (14.6%)	196 (40.8%)
	ABDOMINAL PAIN	37 (7.7%)	26 (5.4%)	63 (13.1%)
	ANOREXIA	3 (0.6%)	0 .	3 (0.6%)
	ANUS DISORDER	3 (0.6%)	0 .	3 (0.6%)
	COLITIS	2 (0.4%)	0 .	2 (0.4%)
	CONSTIPATION	14 (2.9%)	1 (0.2%)	15 (3.1%)
	DIARRHEA	29 (6.0%)	22 (4.6%)	51 (10.6%)
	DIARRHEA BLOODY	1 (0.2%)	0 .	1 (0.2%)
	DIVERTICULITIS	2 (0.4%)	0 .	2 (0.4%)
	DUODENAL ULCER	1 (0.2%)	0 .	1 (0.2%)
	DUODENITIS	2 (0.4%)	0 .	2 (0.4%)
	DYSPEPSIA	23 (4.8%)	12 (2.5%)	35 (7.3%)
	DYSPHAGIA	5 (1.0%)	0 .	5 (1.0%)
	ENTEROCOLITIS	1 (0.2%)	0 .	1 (0.2%)
	ERUCTATION	1 (0.2%)	0 .	1 (0.2%)
	ESOPHAGITIS	5 (1.0%)	0 .	5 (1.0%)
	FLATULENCE	6 (1.3%)	2 (0.4%)	8 (1.7%)
	GASTRIC ULCER	2 (0.4%)	0 .	2 (0.4%)
	GASTRITIS	9 (1.9%)	3 (0.6%)	12 (2.5%)
	GASTROENTERITIS	13 (2.7%)	0 .	13 (2.7%)
	GASTROESOPHAGEAL REFLUX	2 (0.4%)	0 .	2 (0.4%)
	GASTROINTESTINAL DISORDER NOS	7 (1.5%)	0 .	7 (1.5%)
	GI HEMORRHAGE	0 .	1 (0.2%)	1 (0.2%)
	GINGIVITIS	2 (0.4%)	0 .	2 (0.4%)

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INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499 (N= 480)

WHO BODY SYSTEM	WHO PREFERRED TERM	Relationship		Total
		Not-Related	Related	
GASTROINTESTINAL SYSTEM	HEMATEMESIS	2 (0.4%)	0 .	2 (0.4%)
	HEMORRHAGE RECTUM	2 (0.4%)	0 .	2 (0.4%)
	HEMORRHOIDS	8 (1.7%)	0 .	8 (1.7%)
	ILEUS	1 (0.2%)	0 .	1 (0.2%)
	INTESTINAL OBSTRUCTION	4 (0.8%)	0 .	4 (0.8%)
	IRRITABLE BOWEL SYNDROME	1 (0.2%)	0 .	1 (0.2%)
	LACTOSE INTOLERANCE	1 (0.2%)	0 .	1 (0.2%)
	MEGACOLON ACQUIRED	1 (0.2%)	0 .	1 (0.2%)
	MELENA	3 (0.6%)	3 (0.6%)	6 (1.3%)
	NAUSEA	24 (5.0%)	14 (2.9%)	38 (7.9%)
	PANCREATITIS	1 (0.2%)	0 .	1 (0.2%)
	PERIODONTITIS	12 (2.5%)	0 .	12 (2.5%)
	PERITONITIS	1 (0.2%)	0 .	1 (0.2%)
	STOMATITIS	3 (0.6%)	0 .	3 (0.6%)
	TENESMUS	1 (0.2%)	0 .	1 (0.2%)
	TONGUE EDEMA	1 (0.2%)	0 .	1 (0.2%)
	TOOTH ACHE	6 (1.3%)	0 .	6 (1.3%)
	TOOTH DISORDER	1 (0.2%)	0 .	1 (0.2%)
	VOMITING	17 (3.5%)	3 (0.6%)	20 (4.2%)
HEARING AND VESTIBULAR	TOTAL	9 (1.9%)	0 .	9 (1.9%)
	DEAFNESS	2 (0.4%)	0 .	2 (0.4%)
	EAR DISORDER NOS	3 (0.6%)	0 .	3 (0.6%)
	EARACHE	3 (0.6%)	0 .	3 (0.6%)
	HEARING DECREASED	1 (0.2%)	0 .	1 (0.2%)
	TINNITUS	1 (0.2%)	0 .	1 (0.2%)
	VESTIBULAR DISORDER	1 (0.2%)	0 .	1 (0.2%)
HEART RATE AND RHYTHM	TOTAL	41 (8.5%)	7 (1.5%)	48 (10.0%)
	ARRHYTHMIA	3 (0.6%)	0 .	3 (0.6%)
	ARRHYTHMIA ATRIAL	3 (0.6%)	0 .	3 (0.6%)
	ATRIOVENTRICULAR BLOCK	2 (0.4%)	0 .	2 (0.4%)
	BRADYCARDIA	4 (0.8%)	1 (0.2%)	5 (1.0%)
	BUNDLE BRANCH BLOCK	3 (0.6%)	0 .	3 (0.6%)
	CARDIAC ARREST	1 (0.2%)	0 .	1 (0.2%)
	EXTRASYSTOLES	8 (1.7%)	5 (1.0%)	13 (2.7%)

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PROTOCOL 040

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WHO BODY SYSTEM	WHO PREFERRED TERM	Relationship		Total
		Not-Related	Related	
HEART RATE AND RHYTHM	EXTRASYSTOLES	3 (0.6%)	4 (0.8%)	7 (1.5%)
	SUPRAVENTRICULAR FIBRILLATION	9 (1.9%)	0 .	9 (1.9%)
	ATRIAL PALPITATION	3 (0.6%)	1 (0.2%)	4 (0.8%)
	TACHYCARDIA	11 (2.3%)	0 .	11 (2.3%)
	TACHYCARDIA	1 (0.2%)	0 .	1 (0.2%)
	SUPRAVENTRICULAR			
LIVER AND BILIARY SYSTEM	TOTAL	26 (5.4%)	10 (2.1%)	36 (7.5%)
	BILIRUBINEMIA	2 (0.4%)	2 (0.4%)	4 (0.8%)
	CHOLECYSTITIS	2 (0.4%)	0 .	2 (0.4%)
	CHOLELITHIASIS	4 (0.8%)	0 .	4 (0.8%)
	GAMMA-GT INCREASED	6 (1.3%)	3 (0.6%)	9 (1.9%)
	HEPATIC ENZYMES INCREASED	9 (1.9%)	3 (0.6%)	12 (2.5%)
	HEPATIC FUNCTION ABNORMAL	6 (1.3%)	1 (0.2%)	7 (1.5%)
	HEPATITIS	1 (0.2%)	0 .	1 (0.2%)
	LIVER FATTY	1 (0.2%)	0 .	1 (0.2%)
	SGOT INCREASED	4 (0.8%)	1 (0.2%)	5 (1.0%)
	SGPT INCREASED	4 (0.8%)	2 (0.4%)	6 (1.3%)
METABOLIC AND NUTRITIONAL	TOTAL	60 (12.5%)	9 (1.9%)	69 (14.4%)
	BLOOD UREA NITROGEN INCREASED	2 (0.4%)	3 (0.6%)	5 (1.0%)
	DEHYDRATION	2 (0.4%)	0 .	2 (0.4%)
	DIABETES MELLITUS	6 (1.3%)	0 .	6 (1.3%)
	DIABETES MELLITUS AGGRAVATED	3 (0.6%)	0 .	3 (0.6%)
	GLUCOSE TOLERANCE ABNORMAL	0 .	1 (0.2%)	1 (0.2%)
	GLYCOSURIA	4 (0.8%)	0 .	4 (0.8%)
	GOUT	7 (1.5%)	0 .	7 (1.5%)
	HYPERCHOLESTEROLEMIA	3 (0.6%)	0 .	3 (0.6%)
	HYPERGLYCEMIA	21 (4.4%)	2 (0.4%)	23 (4.8%)
	HYPERKALEMIA	1 (0.2%)	1 (0.2%)	2 (0.4%)
	HYPERLIPEMIA	3 (0.6%)	0 .	3 (0.6%)
	HYPERNATREMIA	2 (0.4%)	2 (0.4%)	4 (0.8%)

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INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499 (N= 480)

WHO BODY SYSTEM	WHO PREFERRED TERM	Relationship		Total
		Not-Related	Related	
METABOLIC AND NUTRITIONAL	HYPERURICEMIA	4 (0.8%)	1 (0.2%)	5 (1.0%)
	HYPOCHLOREMIA	1 (0.2%)	0 .	1 (0.2%)
	HYPOGLYCEMIA	5 (1.0%)	0 .	5 (1.0%)
	HYPONATREMIA	1 (0.2%)	0 .	1 (0.2%)
	KETOSIS	1 (0.2%)	0 .	1 (0.2%)
	NPN INCREASED	2 (0.4%)	0 .	2 (0.4%)
	PHOSPHATASE ALKALINE INCREASED	3 (0.6%)	0 .	3 (0.6%)
	WEIGHT DECREASE	11 (2.3%)	0 .	11 (2.3%)
	WEIGHT INCREASE	1 (0.2%)	0 .	1 (0.2%)
MUSCULOSKELETAL SYSTEM	TOTAL	106 (22.1%)	1 (0.2%)	107 (22.3%)
	ARTHRALGIA	30 (6.3%)	0 .	30 (6.3%)
	ARTHRITIS	12 (2.5%)	0 .	12 (2.5%)
	ARTHRITIS AGGRAVATED	1 (0.2%)	0 .	1 (0.2%)
	ARTHROPATHY	2 (0.4%)	0 .	2 (0.4%)
	ARTHROSIS	4 (0.8%)	0 .	4 (0.8%)
	BACK PAIN	56 (11.7%)	0 .	56 (11.7%)
	BONE DEVELOPMENT ABNORMAL	2 (0.4%)	0 .	2 (0.4%)
	BONE DISORDER	2 (0.4%)	0 .	2 (0.4%)
	BURSITIS	2 (0.4%)	0 .	2 (0.4%)
	DUPUYTREN'S CONTRACTURE	1 (0.2%)	0 .	1 (0.2%)
	MYALGIA	12 (2.5%)	1 (0.2%)	13 (2.7%)
	OSTEOPOROSIS	5 (1.0%)	0 .	5 (1.0%)
	SKELETAL PAIN	6 (1.3%)	0 .	6 (1.3%)
	TENDINITIS	3 (0.6%)	0 .	3 (0.6%)
	TENDON DISORDER	1 (0.2%)	0 .	1 (0.2%)
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	TOTAL	18 (3.8%)	0 .	18 (3.8%)
	ANGINA PECTORIS	11 (2.3%)	0 .	11 (2.3%)
	ANGINA PECTORIS AGGRAVATED	2 (0.4%)	0 .	2 (0.4%)
	CARDIOMYOPATHY	1 (0.2%)	0 .	1 (0.2%)

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PROTOCOL 040

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WHO BODY SYSTEM	WHO PREFERRED TERM	Relationship		Total
		Not-Related	Related	
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	CORONARY ARTERY DISORDER	2 (0.4%)	0 .	2 (0.4%)
	MYOCARDIAL INFARCTION	2 (0.4%)	0 .	2 (0.4%)
	MYOCARDIAL ISCHEMIA	2 (0.4%)	0 .	2 (0.4%)
NEOPLASM	TOTAL	26 (5.4%)	1 (0.2%)	27 (5.6%)
	ADENOCARCINOMA NOS	1 (0.2%)	0 .	1 (0.2%)
	BASAL CELL CARCINOMA	1 (0.2%)	0 .	1 (0.2%)
	BREAST FIBROADENOSIS	1 (0.2%)	0 .	1 (0.2%)
	BREAST NEOPLASM FEMALE	2 (0.4%)	0 .	2 (0.4%)
	CARCINOMA	2 (0.4%)	0 .	2 (0.4%)
	GI NEOPLASM MALIGNANT	1 (0.2%)	0 .	1 (0.2%)
	HEMANGIOMA ACQUIRED	1 (0.2%)	0 .	1 (0.2%)
	HEPATIC NEOPLASM	1 (0.2%)	0 .	1 (0.2%)
	LIPOMA	1 (0.2%)	0 .	1 (0.2%)
	NEOPLASM NOS	8 (1.7%)	1 (0.2%)	9 (1.9%)
	PULMONARY CARCINOMA	7 (1.5%)	0 .	7 (1.5%)
PLATELET BLEEDING AND CLOTTING	TOTAL	5 (1.0%)	0 .	5 (1.0%)
	HEMATOMA	1 (0.2%)	0 .	1 (0.2%)
	PURPURA	2 (0.4%)	0 .	2 (0.4%)
	THROMBOCYTOPENIA	2 (0.4%)	0 .	2 (0.4%)
PSYCHIATRIC	TOTAL	53 (11.0%)	4 (0.8%)	57 (11.9%)
	AGITATION	2 (0.4%)	0 .	2 (0.4%)
	AMNESIA	1 (0.2%)	0 .	1 (0.2%)
	ANXIETY	12 (2.5%)	0 .	12 (2.5%)
	CONFUSION	2 (0.4%)	1 (0.2%)	3 (0.6%)
	DEPRESSION	21 (4.4%)	0 .	21 (4.4%)
	DEPRESSION AGGRAVATED	1 (0.2%)	0 .	1 (0.2%)
	INSOMNIA	21 (4.4%)	2 (0.4%)	23 (4.8%)
	NERVOUSNESS	1 (0.2%)	1 (0.2%)	2 (0.4%)
	SOMNOLENCE	3 (0.6%)	0 .	3 (0.6%)
	SUICIDE ATTEMPT	1 (0.2%)	0 .	1 (0.2%)
RED BLOOD CELL	TOTAL	15 (3.1%)	1 (0.2%)	16 (3.3%)
	ANEMIA	7 (1.5%)	1 (0.2%)	8 (1.7%)
	ANEMIA HYPOCHROMIC	1 (0.2%)	0 .	1 (0.2%)

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		Not-Related	Related	
RED BLOOD CELL	ERYTHROCYTES ABNORMAL	1 (0.2%)	0 .	1 (0.2%)
	POLYCYTHEMIA	6 (1.3%)	0 .	6 (1.3%)
REPRODUCTIVE FEMALE	TOTAL	5 (1.0%)	0 .	5 (1.0%)
	MENSTRUAL DISORDER	1 (0.2%)	0 .	1 (0.2%)
	VAGINAL HEMORRHAGE	1 (0.2%)	0 .	1 (0.2%)
	VAGINITIS	3 (0.6%)	0 .	3 (0.6%)
REPRODUCTIVE MALE	TOTAL	13 (2.7%)	0 .	13 (2.7%)
	IMPOTENCE	6 (1.3%)	0 .	6 (1.3%)
	PROSTATIC DISORDER	6 (1.3%)	0 .	6 (1.3%)
	TESTIS DISORDER	1 (0.2%)	0 .	1 (0.2%)
RESISTANCE MECHANISM	TOTAL	110 (22.9%)	1 (0.2%)	111 (23.1%)
	ABSCCESS	4 (0.8%)	0 .	4 (0.8%)
	HERPES SIMPLEX	3 (0.6%)	0 .	3 (0.6%)
	HERPES ZOSTER	8 (1.7%)	0 .	8 (1.7%)
	INFECTION	11 (2.3%)	0 .	11 (2.3%)
	INFECTION BACTERIAL	2 (0.4%)	0 .	2 (0.4%)
	INFECTION FUNGAL	2 (0.4%)	0 .	2 (0.4%)
	INFECTION VIRAL	38 (7.9%)	1 (0.2%)	39 (8.1%)
	MONILIASIS	6 (1.3%)	0 .	6 (1.3%)
	MONILIASIS GENITAL	1 (0.2%)	0 .	1 (0.2%)
	OTITIS MEDIA	5 (1.0%)	0 .	5 (1.0%)
	SEPSIS	2 (0.4%)	0 .	2 (0.4%)
	UPPER RESP TRACT INFECTION	50 (10.4%)	1 (0.2%)	51 (10.6%)
RESPIRATORY SYSTEM	TOTAL	349 (72.7%)	8 (1.7%)	357 (74.4%)
	APNEA	1 (0.2%)	0 .	1 (0.2%)
	ASTHMA	1 (0.2%)	0 .	1 (0.2%)
	BRONCHITIS	14 (2.9%)	0 .	14 (2.9%)
	CHEST X-RAY ABNORMAL	3 (0.6%)	0 .	3 (0.6%)
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	320 (66.7%)	7 (1.5%)	327 (68.1%)
	COUGHING	30 (6.3%)	1 (0.2%)	31 (6.5%)
	DYSYPNEA	13 (2.7%)	0 .	13 (2.7%)
	EPISTAXIS	3 (0.6%)	0 .	3 (0.6%)
	HEMOPTYSIS	6 (1.3%)	1 (0.2%)	7 (1.5%)

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SB 207499

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, BODY SYSTEM,
PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499 (N= 480)

WHO BODY SYSTEM	WHO PREFERRED TERM	Relationship		Total
		Not-Related	Related	
RESPIRATORY SYSTEM	HYPOXIA	1 (0.2%)	0 .	1 (0.2%)
	LARYNGITIS	2 (0.4%)	0 .	2 (0.4%)
	PHARYNGITIS	42 (8.8%)	0 .	42 (8.8%)
	PLEURAL EFFUSION	1 (0.2%)	0 .	1 (0.2%)
	PLEURAL PAIN	2 (0.4%)	0 .	2 (0.4%)
	PLEURISY	2 (0.4%)	0 .	2 (0.4%)
	PNEUMONIA	14 (2.9%)	0 .	14 (2.9%)
	PNEUMONIA LOBAR	1 (0.2%)	0 .	1 (0.2%)
	RESPIRATORY DISORDER	28 (5.8%)	0 .	28 (5.8%)
	RESPIRATORY	3 (0.6%)	0 .	3 (0.6%)
	INSUFFICIENCY			
	RHINITIS	44 (9.2%)	0 .	44 (9.2%)
	SINUSITIS	16 (3.3%)	0 .	16 (3.3%)
	SPUTUM INCREASED	6 (1.3%)	0 .	6 (1.3%)
	TRACHEITIS	3 (0.6%)	0 .	3 (0.6%)
SKIN AND APPENDAGES	TOTAL	43 (9.0%)	4 (0.8%)	47 (9.8%)
	ALOPECIA	2 (0.4%)	0 .	2 (0.4%)
	ANGIOEDEMA	1 (0.2%)	0 .	1 (0.2%)
	BULLOUS ERUPTION	1 (0.2%)	0 .	1 (0.2%)
	DERMATITIS	5 (1.0%)	1 (0.2%)	6 (1.3%)
	DERMATITIS FUNGAL	1 (0.2%)	0 .	1 (0.2%)
	DERMATITIS LICHENOID	2 (0.4%)	0 .	2 (0.4%)
	ECZEMA	5 (1.0%)	0 .	5 (1.0%)
	FOLLICULITIS	2 (0.4%)	0 .	2 (0.4%)
	HYPERKERATOSIS	1 (0.2%)	0 .	1 (0.2%)
	MELANOSIS	1 (0.2%)	0 .	1 (0.2%)
	PRURITUS	14 (2.9%)	0 .	14 (2.9%)
	PSORIASIS	1 (0.2%)	0 .	1 (0.2%)
	RASH	4 (0.8%)	1 (0.2%)	5 (1.0%)
	RASH ERYTHEMATOUS	1 (0.2%)	0 .	1 (0.2%)
	RASH MACULO-PAPULAR	3 (0.6%)	0 .	3 (0.6%)
	RASH PUSTULAR	1 (0.2%)	0 .	1 (0.2%)
	SKIN DISORDER	5 (1.0%)	0 .	5 (1.0%)
	SKIN DRY	2 (0.4%)	0 .	2 (0.4%)
	SKIN HYPERTROPHY	1 (0.2%)	0 .	1 (0.2%)
	SKIN ULCERATION	4 (0.8%)	0 .	4 (0.8%)
	URTICARIA	5 (1.0%)	2 (0.4%)	7 (1.5%)

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INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499 (N= 480)

WHO BODY SYSTEM	WHO PREFERRED TERM	Relationship		Total
		Not-Related	Related	
SPECIAL SENSES OTHER	TOTAL	0	2 (0.4%)	2 (0.4%)
	TASTE PERVERSION	0	2 (0.4%)	2 (0.4%)
URINARY SYSTEM	TOTAL	64 (13.3%)	1 (0.2%)	65 (13.5%)
	ALBUMINURIA	12 (2.5%)	.	12 (2.5%)
	BLADDER CALCULUS	1 (0.2%)	0	1 (0.2%)
	CYSTITIS	5 (1.0%)	0	5 (1.0%)
	DYSURIA	3 (0.6%)	0	3 (0.6%)
	HEMATURIA	13 (2.7%)	0	13 (2.7%)
	MICTURITION DISORDER	1 (0.2%)	0	1 (0.2%)
	MICTURITION FREQUENCY	3 (0.6%)	0	3 (0.6%)
	NOCTURIA	1 (0.2%)	0	1 (0.2%)
	PYELONEPHRITIS	2 (0.4%)	0	2 (0.4%)
	PYURIA	11 (2.3%)	1 (0.2%)	12 (2.5%)
	RENAL CALCULUS	1 (0.2%)	0	1 (0.2%)
	RENAL CYST	1 (0.2%)	0	1 (0.2%)
	RENAL FAILURE ACUTE	2 (0.4%)	0	2 (0.4%)
	RENAL FUNCTION ABNORMAL	1 (0.2%)	0	1 (0.2%)
	RENAL PAIN	3 (0.6%)	0	3 (0.6%)
	URINARY INCONTINENCE	2 (0.4%)	0	2 (0.4%)
	URINARY RETENTION	4 (0.8%)	0	4 (0.8%)
	URINARY TRACT INFECTION	22 (4.6%)	0	22 (4.6%)
	URINE ABNORMAL	1 (0.2%)	0	1 (0.2%)
VASCULAR EXTRACARDIAC	TOTAL	20 (4.2%)	0	20 (4.2%)
	ARTERIOSCLEROSIS	1 (0.2%)	0	1 (0.2%)
	CEREBROVASCULAR DISORDER	4 (0.8%)	0	4 (0.8%)
	CLAUDICATION INTERMITTENT	1 (0.2%)	0	1 (0.2%)
	CRAMPS LEGS	2 (0.4%)	0	2 (0.4%)
	PERIPHERAL ISCHEMIA	1 (0.2%)	0	1 (0.2%)
	PHLEBITIS	1 (0.2%)	0	1 (0.2%)
	PHLEBITIS SUPERFICIAL	1 (0.2%)	0	1 (0.2%)
	THROMBOPHLEBITIS LEG	1 (0.2%)	0	1 (0.2%)

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TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, BODY SYSTEM,
PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499 (N= 480)

WHO BODY SYSTEM	WHO PREFERRED TERM	Relationship		Total
		Not-Related	Related	
VASCULAR EXTRACARDIAC	THROMBOPHLEBITIS	1 (0.2%)	0 .	1 (0.2%)
	RETINAL VEIN THROMBOSIS ARTERIAL LEG	1 (0.2%)	0 .	1 (0.2%)
	THROMBOSIS RETINAL ARTERY	2 (0.4%)	0 .	2 (0.4%)
	VASCULAR DISORDER	3 (0.6%)	0 .	3 (0.6%)
	VEIN DISORDER	1 (0.2%)	0 .	1 (0.2%)
	VEIN VARICOSE	3 (0.6%)	0 .	3 (0.6%)
	TOTAL	21 (4.4%)	0 .	21 (4.4%)
VISION	BLEPHARITIS	1 (0.2%)	0 .	1 (0.2%)
	CATARACT	6 (1.3%)	0 .	6 (1.3%)
	CONJUNCTIVAL HEMORRHAGE	1 (0.2%)	0 .	1 (0.2%)
	CONJUNCTIVITIS	8 (1.7%)	0 .	8 (1.7%)
	CORNEAL ULCERATION	1 (0.2%)	0 .	1 (0.2%)
	EYE ABNORMALITY	2 (0.4%)	0 .	2 (0.4%)
	GLAUCOMA	1 (0.2%)	0 .	1 (0.2%)
	UVEITIS	1 (0.2%)	0 .	1 (0.2%)
	VISION ABNORMAL	1 (0.2%)	0 .	1 (0.2%)
	VISUAL FIELD DEFECT	1 (0.2%)	0 .	1 (0.2%)
WHITE CELL AND RETICULOENDOTHELIAL SYSTE	TOTAL	23 (4.8%)	0 .	23 (4.8%)
	EOSINOPHILIA	2 (0.4%)	0 .	2 (0.4%)
	GRANULOCYTOPENIA	2 (0.4%)	0 .	2 (0.4%)
	LEUKOCYTOSIS	17 (3.5%)	0 .	17 (3.5%)
	LEUKOPENIA	2 (0.4%)	0 .	2 (0.4%)
	LYMPHADENOPATHY	2 (0.4%)	0 .	2 (0.4%)
	LYMPHADENOPATHY CERVICAL	1 (0.2%)	0 .	1 (0.2%)
	LYMPHOPENIA	1 (0.2%)	0 .	1 (0.2%)

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TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL (N= 723)

WHO BODY SYSTEM	WHO PREFERRED TERM	----- Relationship -----		-----	
		Not-Related	Related	Total	
TOTAL	TOTAL	482 (66.7%)	193 (26.7%)	675 (93.4%)	
APPLICATION SITE	TOTAL	8 (1.1%)	0 .	8 (1.1%)	
	INJECTION SITE	1 (0.1%)	0 .	1 (0.1%)	
	INFLAMMATION				
	OTITIS EXTERNA	8 (1.1%)	0 .	8 (1.1%)	
	TYMPANIC MEMBRANE PERFORATION	1 (0.1%)	0 .	1 (0.1%)	
AUTONOMIC NERVOUS SYSTEM	TOTAL	5 (0.7%)	2 (0.3%)	7 (1.0%)	
	MOUTH DRY	3 (0.4%)	0 .	3 (0.4%)	
	SWEATING INCREASED	2 (0.3%)	2 (0.3%)	4 (0.6%)	
BODY AS A WHOLE GENERAL	TOTAL	195 (27.0%)	9 (1.2%)	204 (28.2%)	
	ALCOHOL INTOLERANCE	1 (0.1%)	0 .	1 (0.1%)	
	ALLERGIC REACTION	4 (0.6%)	0 .	4 (0.6%)	
	ASTHENIA	21 (2.9%)	2 (0.3%)	23 (3.2%)	
	CELLULITIS	5 (0.7%)	0 .	5 (0.7%)	
	CHEST PAIN	40 (5.5%)	1 (0.1%)	41 (5.7%)	
	CHEST PAIN PRECORDIAL	6 (0.8%)	0 .	6 (0.8%)	
	CHEST PAIN SUBSTERNAL	2 (0.3%)	0 .	2 (0.3%)	
	DRUG LEVEL INCREASED	1 (0.1%)	0 .	1 (0.1%)	
	EDEMA	1 (0.1%)	0 .	1 (0.1%)	
	EDEMA DEPENDENT	7 (1.0%)	0 .	7 (1.0%)	
	EDEMA LEGS	10 (1.4%)	0 .	10 (1.4%)	
	FACE EDEMA	0 .	1 (0.1%)	1 (0.1%)	
	FATIGUE	13 (1.8%)	4 (0.6%)	17 (2.4%)	
	FEVER	19 (2.6%)	0 .	19 (2.6%)	
	HOT FLUSHES	1 (0.1%)	0 .	1 (0.1%)	
	INFLUENZA-LIKE SYMPTOMS	4 (0.6%)	0 .	4 (0.6%)	
	INJURY	88 (12.2%)	0 .	88 (12.2%)	
	MALAISE	14 (1.9%)	2 (0.3%)	16 (2.2%)	
	PAIN	31 (4.3%)	0 .	31 (4.3%)	
	RIGORS	2 (0.3%)	0 .	2 (0.3%)	
	THERAPEUTIC RESPONSE INCREASED	3 (0.4%)	0 .	3 (0.4%)	

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INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL (N= 723)

WHO BODY SYSTEM	WHO PREFERRED TERM	Relationship		Total
		Not-Related	Related	
CARDIOVASCULAR GENERAL	TOTAL	76 (10.5%)	5 (0.7%)	81 (11.2%)
	ANEURYSM	3 (0.4%)	0 .	3 (0.4%)
	CARDIAC FAILURE	5 (0.7%)	0 .	5 (0.7%)
	CARDIOMEGALY	3 (0.4%)	0 .	3 (0.4%)
	COR PULMONALE	1 (0.1%)	0 .	1 (0.1%)
	CYANOSIS	1 (0.1%)	0 .	1 (0.1%)
	ECG ABNORMAL	3 (0.4%)	0 .	3 (0.4%)
	ECG ABNORMAL SPECIFIC	3 (0.4%)	0 .	3 (0.4%)
	HEART VALVE DISORDERS	1 (0.1%)	0 .	1 (0.1%)
	HYPERTENSION	40 (5.5%)	2 (0.3%)	42 (5.8%)
	HYPERTENSION AGGRAVATED	8 (1.1%)	0 .	8 (1.1%)
	HYPERTENSION PULMONARY	1 (0.1%)	0 .	1 (0.1%)
	HYPOTENSION	4 (0.6%)	2 (0.3%)	6 (0.8%)
	HYPOTENSION POSTURAL	4 (0.6%)	1 (0.1%)	5 (0.7%)
	SYNCOPE	12 (1.7%)	0 .	12 (1.7%)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	TOTAL	124 (17.2%)	29 (4.0%)	153 (21.2%)
	ATAXIA	1 (0.1%)	0 .	1 (0.1%)
	COMA	1 (0.1%)	0 .	1 (0.1%)
	CONVULSIONS	2 (0.3%)	0 .	2 (0.3%)
	DIZZINESS	24 (3.3%)	10 (1.4%)	34 (4.7%)
	DYSPHONIA	5 (0.7%)	0 .	5 (0.7%)
	EXTRAPYRAMIDAL DISORDER	2 (0.3%)	0 .	2 (0.3%)
	HEADACHE	60 (8.3%)	19 (2.6%)	79 (10.9%)
	HYPERTONIA	4 (0.6%)	0 .	4 (0.6%)
	HYPESTHESIA	1 (0.1%)	0 .	1 (0.1%)
	MIGRAINE	4 (0.6%)	0 .	4 (0.6%)
	MUSCLE CONTRACTIONS INVOLUNTARY	3 (0.4%)	0 .	3 (0.4%)
	NERVE ROOT LESION	1 (0.1%)	0 .	1 (0.1%)
	NEURALGIA	18 (2.5%)	0 .	18 (2.5%)
	NEUROPATHY	1 (0.1%)	0 .	1 (0.1%)
	NEUROPATHY PERIPHERAL	2 (0.3%)	0 .	2 (0.3%)
	PARESIS	3 (0.4%)	0 .	3 (0.4%)
	PARESTHESIA	4 (0.6%)	0 .	4 (0.6%)

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PROTOCOL 040

PRIOR TREATMENT: TOTAL (N= 723)

WHO BODY SYSTEM	WHO PREFERRED TERM	Relationship		Total
		Not-Related	Related	
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	PARKINSONISM AGGRAVATED	1 (0.1%)	0 .	1 (0.1%)
	TREMOR	4 (0.6%)	2 (0.3%)	6 (0.8%)
	TRIGEMINAL NEURALGIA	1 (0.1%)	0 .	1 (0.1%)
	VERTIGO	17 (2.4%)	1 (0.1%)	18 (2.5%)
	WITHDRAWAL HEADACHE	1 (0.1%)	0 .	1 (0.1%)
COLLAGEN	TOTAL	3 (0.4%)	0 .	3 (0.4%)
	ARTHRITIS RHEUMATOID	2 (0.3%)	0 .	2 (0.3%)
	ARTHRITIS RHEUMATOID AGGRAVATED	1 (0.1%)	0 .	1 (0.1%)
ENDOCRINE	TOTAL	13 (1.8%)	0 .	13 (1.8%)
	GOITRE	2 (0.3%)	0 .	2 (0.3%)
	HYPERTHYROIDISM	7 (1.0%)	0 .	7 (1.0%)
	HYPOTHYROIDISM	3 (0.4%)	0 .	3 (0.4%)
	MASTITIS MALE	1 (0.1%)	0 .	1 (0.1%)
	SIALOADENITIS	1 (0.1%)	0 .	1 (0.1%)
FETAL	THYROIDITIS	1 (0.1%)	0 .	1 (0.1%)
	TOTAL	1 (0.1%)	0 .	1 (0.1%)
GASTROINTESTINAL SYSTEM	SPINE MALFORMATION	1 (0.1%)	0 .	1 (0.1%)
	TOTAL	186 (25.7%)	144 (19.9%)	330 (45.6%)
	ABDOMINAL PAIN	52 (7.2%)	61 (8.4%)	113 (15.6%)
	ANOREXIA	7 (1.0%)	3 (0.4%)	10 (1.4%)
	ANUS DISORDER	3 (0.4%)	0 .	3 (0.4%)
	APPETITE INCREASED	1 (0.1%)	0 .	1 (0.1%)
	COLITIS	2 (0.3%)	0 .	2 (0.3%)
	CONSTIPATION	19 (2.6%)	1 (0.1%)	20 (2.8%)
	DIARRHEA	50 (6.9%)	45 (6.2%)	95 (13.1%)
	DIARRHEA BLOODY	1 (0.1%)	0 .	1 (0.1%)
	DIVERTICULITIS	2 (0.3%)	0 .	2 (0.3%)
	DUODENAL ULCER	1 (0.1%)	0 .	1 (0.1%)
	DUODENITIS	3 (0.4%)	0 .	3 (0.4%)
	DYSPEPSIA	36 (5.0%)	29 (4.0%)	65 (9.0%)
	DYSPHAGIA	5 (0.7%)	0 .	5 (0.7%)
	ENTERITIS	2 (0.3%)	0 .	2 (0.3%)

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PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL (N= 723)

WHO BODY SYSTEM	WHO PREFERRED TERM	Relationship		Total
		Not-Related	Related	
GASTROINTESTINAL SYSTEM	ENTEROCOLITIS	1 (0.1%)	0 .	1 (0.1%)
	ERUCTION	1 (0.1%)	0 .	1 (0.1%)
	ESOPHAGITIS	7 (1.0%)	1 (0.1%)	8 (1.1%)
	ESOPHAGOSPASM	1 (0.1%)	0 .	1 (0.1%)
	FLATULENCE	11 (1.5%)	2 (0.3%)	13 (1.8%)
	GASTRIC ULCER	2 (0.3%)	0 .	2 (0.3%)
	GASTRITIS	13 (1.8%)	5 (0.7%)	18 (2.5%)
	GASTROENTERITIS	24 (3.3%)	0 .	24 (3.3%)
	GASTROESOPHAGEAL REFLUX	4 (0.6%)	1 (0.1%)	5 (0.7%)
	GASTROINTESTINAL DISORDER NOS	11 (1.5%)	1 (0.1%)	12 (1.7%)
	GI HEMORRHAGE	2 (0.3%)	2 (0.3%)	4 (0.6%)
	GINGIVITIS	2 (0.3%)	0 .	2 (0.3%)
	HEMATEMESIS	2 (0.3%)	0 .	2 (0.3%)
	HEMORRHAGE RECTUM	3 (0.4%)	0 .	3 (0.4%)
	HEMORRHOIDS	10 (1.4%)	0 .	10 (1.4%)
	ILEUS	1 (0.1%)	0 .	1 (0.1%)
	INTESTINAL OBSTRUCTION	5 (0.7%)	0 .	5 (0.7%)
	IRRITABLE BOWEL SYNDROME	2 (0.3%)	0 .	2 (0.3%)
	LACTOSE INTOLERANCE	1 (0.1%)	0 .	1 (0.1%)
	MEGACOLON ACQUIRED	1 (0.1%)	0 .	1 (0.1%)
	MELENA	6 (0.8%)	5 (0.7%)	11 (1.5%)
	NAUSEA	36 (5.0%)	36 (5.0%)	72 (10.0%)
	PANCREATITIS	1 (0.1%)	1 (0.1%)	2 (0.3%)
	PERIODONTITIS	17 (2.4%)	0 .	17 (2.4%)
	PERITONITIS	1 (0.1%)	0 .	1 (0.1%)
	PROCTITIS	1 (0.1%)	0 .	1 (0.1%)
	STOMATITIS	4 (0.6%)	0 .	4 (0.6%)
	TENESMUS	1 (0.1%)	0 .	1 (0.1%)
	TONGUE EDEMA	1 (0.1%)	0 .	1 (0.1%)
	TOOTH ACHE	8 (1.1%)	0 .	8 (1.1%)
	TOOTH CARIES	2 (0.3%)	0 .	2 (0.3%)
	TOOTH DISORDER	2 (0.3%)	0 .	2 (0.3%)
	VOMITING	20 (2.8%)	15 (2.1%)	35 (4.8%)
HEARING AND VESTIBULAR	TOTAL	17 (2.4%)	0 .	17 (2.4%)

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4. NOT RELATED=UNLIKELY OR NOT-RELATED TO TREATMENT, RELATED=SUSPECTED OR PROBABLY RELATED TO TREATMENT

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, BODY SYSTEM,
PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL (N= 723)

WHO BODY SYSTEM	WHO PREFERRED TERM	Relationship		Total
		Not-Related	Related	
HEARING AND VESTIBULAR	DEAFNESS	3 (0.4%)	0 .	3 (0.4%)
	EAR DISORDER NOS	6 (0.8%)	0 .	6 (0.8%)
	EARACHE	4 (0.6%)	0 .	4 (0.6%)
	HEARING DECREASED	1 (0.1%)	0 .	1 (0.1%)
	TINNITUS	3 (0.4%)	0 .	3 (0.4%)
	VESTIBULAR DISORDER	2 (0.3%)	0 .	2 (0.3%)
HEART RATE AND RHYTHM	TOTAL	66 (9.1%)	13 (1.8%)	79 (10.9%)
	ARRHYTHMIA	7 (1.0%)	0 .	7 (1.0%)
	ARRHYTHMIA ATRIAL	4 (0.6%)	0 .	4 (0.6%)
	ATRIOVENTRICULAR BLOCK	2 (0.3%)	0 .	2 (0.3%)
	BRADYCARDIA	9 (1.2%)	3 (0.4%)	12 (1.7%)
	BUNDLE BRANCH BLOCK	5 (0.7%)	0 .	5 (0.7%)
	CARDIAC ARREST	1 (0.1%)	0 .	1 (0.1%)
	EXTRASYSTOLES	11 (1.5%)	6 (0.8%)	17 (2.4%)
	EXTRASYSTOLES SUPRAVENTRICULAR	6 (0.8%)	6 (0.8%)	12 (1.7%)
	FIBRILLATION ATRIAL	11 (1.5%)	1 (0.1%)	12 (1.7%)
	PALPITATION	3 (0.4%)	1 (0.1%)	4 (0.6%)
	QT INCREASED	1 (0.1%)	0 .	1 (0.1%)
	TACHYCARDIA	20 (2.8%)	1 (0.1%)	21 (2.9%)
	TACHYCARDIA SUPRAVENTRICULAR	1 (0.1%)	0 .	1 (0.1%)
LIVER AND BILIARY SYSTEM	TOTAL	36 (5.0%)	13 (1.8%)	49 (6.8%)
	BILIRUBINEMIA	2 (0.3%)	3 (0.4%)	5 (0.7%)
	CHOLECYSTITIS	2 (0.3%)	0 .	2 (0.3%)
	CHOLELITHIASIS	6 (0.8%)	0 .	6 (0.8%)
	GAMMA-GT INCREASED	11 (1.5%)	5 (0.7%)	16 (2.2%)
	HEPATIC CIRRHOSIS	1 (0.1%)	0 .	1 (0.1%)
	HEPATIC ENZYMES INCREASED	11 (1.5%)	4 (0.6%)	15 (2.1%)
	HEPATIC FUNCTION ABNORMAL	6 (0.8%)	1 (0.1%)	7 (1.0%)
	HEPATITIS	1 (0.1%)	0 .	1 (0.1%)
	HEPATITIS INFECTIOUS	1 (0.1%)	0 .	1 (0.1%)
	LIVER FATTY	1 (0.1%)	0 .	1 (0.1%)

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INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL (N= 723)

WHO BODY SYSTEM	WHO PREFERRED TERM	Relationship		Total
		Not-Related	Related	
LIVER AND BILIARY SYSTEM	SGOT INCREASED	4 (0.6%)	1 (0.1%)	5 (0.7%)
	SGPT INCREASED	4 (0.6%)	3 (0.4%)	7 (1.0%)
METABOLIC AND NUTRITIONAL	TOTAL	91 (12.6%)	14 (1.9%)	105 (14.5%)
	BLOOD UREA NITROGEN INCREASED	2 (0.3%)	3 (0.4%)	5 (0.7%)
	DEHYDRATION	2 (0.3%)	0 .	2 (0.3%)
	DIABETES MELLITUS	8 (1.1%)	0 .	8 (1.1%)
	DIABETES MELLITUS AGGRAVATED	3 (0.4%)	0 .	3 (0.4%)
	GLUCOSE TOLERANCE ABNORMAL	0 .	1 (0.1%)	1 (0.1%)
	GLYCOSURIA	8 (1.1%)	0 .	8 (1.1%)
	GOUT	12 (1.7%)	0 .	12 (1.7%)
	HYPERCHOLESTEROLEMIA	7 (1.0%)	0 .	7 (1.0%)
	HYPERGLYCEMIA	28 (3.9%)	3 (0.4%)	31 (4.3%)
	HYPERKALEMIA	1 (0.1%)	2 (0.3%)	3 (0.4%)
	HYPERLIPEMIA	3 (0.4%)	0 .	3 (0.4%)
	HYPERNATREMIA	2 (0.3%)	3 (0.4%)	5 (0.7%)
	HYPERTRIGLYCERIDEMIA	1 (0.1%)	0 .	1 (0.1%)
	HYPERURICEMIA	7 (1.0%)	1 (0.1%)	8 (1.1%)
	HYPOCHLOREMIA	2 (0.3%)	0 .	2 (0.3%)
	HYPOGLYCEMIA	6 (0.8%)	0 .	6 (0.8%)
	HYPOKALEMIA	1 (0.1%)	1 (0.1%)	2 (0.3%)
	HYPONATREMIA	3 (0.4%)	0 .	3 (0.4%)
	KETOSIS	1 (0.1%)	0 .	1 (0.1%)
	NPN INCREASED	2 (0.3%)	0 .	2 (0.3%)
	OBESITY	1 (0.1%)	0 .	1 (0.1%)
	PHOSPHATASE ALKALINE INCREASED	3 (0.4%)	0 .	3 (0.4%)
	WEIGHT DECREASE	18 (2.5%)	2 (0.3%)	20 (2.8%)
	WEIGHT INCREASE	2 (0.3%)	0 .	2 (0.3%)
MUSCULOSKELETAL SYSTEM	TOTAL	166 (23.0%)	1 (0.1%)	167 (23.1%)
	ARTHRALGIA	50 (6.9%)	0 .	50 (6.9%)
	ARTHRITIS	19 (2.6%)	0 .	19 (2.6%)
	ARTHRITIS AGGRAVATED	3 (0.4%)	0 .	3 (0.4%)

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INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, BODY SYSTEM,
PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL (N= 723)

WHO BODY SYSTEM	WHO PREFERRED TERM	Relationship		Total
		Not-Related	Related	
MUSCULOSKELETAL SYSTEM	ARTHROPATHY	4 (0.6%)	0 .	4 (0.6%)
	ARTHROSIS	6 (0.8%)	0 .	6 (0.8%)
	BACK PAIN	79 (10.9%)	0 .	79 (10.9%)
	BONE DEVELOPMENT ABNORMAL	2 (0.3%)	0 .	2 (0.3%)
	BONE DISORDER	2 (0.3%)	0 .	2 (0.3%)
	BURSITIS	2 (0.3%)	0 .	2 (0.3%)
	DUPUYTREN'S CONTRACTURE	1 (0.1%)	0 .	1 (0.1%)
	MYALGIA	25 (3.5%)	1 (0.1%)	26 (3.6%)
	MYOSITIS	1 (0.1%)	0 .	1 (0.1%)
	OSTEONECROSIS	1 (0.1%)	0 .	1 (0.1%)
	OSTEOPOROSIS	6 (0.8%)	0 .	6 (0.8%)
	SKELETAL PAIN	8 (1.1%)	0 .	8 (1.1%)
	TENDINITIS	3 (0.4%)	0 .	3 (0.4%)
	TENDON DISORDER	2 (0.3%)	0 .	2 (0.3%)
	TOTAL	27 (3.7%)	0 .	27 (3.7%)
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	ANGINA PECTORIS	18 (2.5%)	0 .	18 (2.5%)
	ANGINA PECTORIS AGGRAVATED	2 (0.3%)	0 .	2 (0.3%)
	AORTIC STENOSIS	1 (0.1%)	0 .	1 (0.1%)
	CARDIOMYOPATHY	1 (0.1%)	0 .	1 (0.1%)
	CORONARY ARTERY DISORDER	2 (0.3%)	0 .	2 (0.3%)
	MYOCARDIAL INFARCTION	3 (0.4%)	0 .	3 (0.4%)
	MYOCARDIAL ISCHEMIA	2 (0.3%)	0 .	2 (0.3%)
	TOTAL	49 (6.8%)	1 (0.1%)	50 (6.9%)
NEOPLASM	ADENOCARCINOMA NOS	2 (0.3%)	0 .	2 (0.3%)
	BASAL CELL CARCINOMA	2 (0.3%)	0 .	2 (0.3%)
	BLADDER CARCINOMA	2 (0.3%)	0 .	2 (0.3%)
	BREAST FIBROADENOSIS	1 (0.1%)	0 .	1 (0.1%)
	BREAST NEOPLASM FEMALE	2 (0.3%)	0 .	2 (0.3%)
	CARCINOMA	5 (0.7%)	0 .	5 (0.7%)
	COLON CARCINOMA	1 (0.1%)	0 .	1 (0.1%)
	GASTRIC CARCINOMA	1 (0.1%)	0 .	1 (0.1%)

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INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL (N= 723)

WHO BODY SYSTEM	WHO PREFERRED TERM	Relationship		Total
		Not-Related	Related	
NEOPLASM	GI NEOPLASM MALIGNANT	1 (0.1%)	0 .	1 (0.1%)
	HEMANGIOMA ACQUIRED	1 (0.1%)	0 .	1 (0.1%)
	HEPATIC NEOPLASM	1 (0.1%)	0 .	1 (0.1%)
	LIPOMA	3 (0.4%)	0 .	3 (0.4%)
	LYMPHOMA MALIGNANT	1 (0.1%)	0 .	1 (0.1%)
	NEOPLASM MALIGNANT	1 (0.1%)	0 .	1 (0.1%)
	NEOPLASM NOS	18 (2.5%)	1 (0.1%)	19 (2.6%)
	PULMONARY CARCINOMA	8 (1.1%)	0 .	8 (1.1%)
PLATELET BLEEDING AND CLOTTING	TOTAL	6 (0.8%)	0 .	6 (0.8%)
	HEMATOMA	1 (0.1%)	0 .	1 (0.1%)
	PURPURA	3 (0.4%)	0 .	3 (0.4%)
	THROMBOCYTOPENIA	2 (0.3%)	0 .	2 (0.3%)
PSYCHIATRIC	TOTAL	84 (11.6%)	8 (1.1%)	92 (12.7%)
	AGITATION	4 (0.6%)	0 .	4 (0.6%)
	AMNESIA	1 (0.1%)	0 .	1 (0.1%)
	ANXIETY	24 (3.3%)	1 (0.1%)	25 (3.5%)
	APATHY	1 (0.1%)	0 .	1 (0.1%)
	CONCENTRATION IMPAIRED	1 (0.1%)	0 .	1 (0.1%)
	CONFUSION	2 (0.3%)	1 (0.1%)	3 (0.4%)
	DEPRESSION	31 (4.3%)	0 .	31 (4.3%)
	DEPRESSION AGGRAVATED	1 (0.1%)	0 .	1 (0.1%)
	INSOMNIA	28 (3.9%)	3 (0.4%)	31 (4.3%)
	NERVOUSNESS	4 (0.6%)	3 (0.4%)	7 (1.0%)
	SOMNOLENCE	7 (1.0%)	0 .	7 (1.0%)
	SUICIDE ATTEMPT	1 (0.1%)	0 .	1 (0.1%)
RED BLOOD CELL	TOTAL	18 (2.5%)	1 (0.1%)	19 (2.6%)
	ANEMIA	9 (1.2%)	1 (0.1%)	10 (1.4%)
	ANEMIA HYPOCHROMIC	1 (0.1%)	0 .	1 (0.1%)
	ANEMIA MACROCYTIC	1 (0.1%)	0 .	1 (0.1%)
	ERYTHROCYTES ABNORMAL	1 (0.1%)	0 .	1 (0.1%)
	POLYCYTHEMIA	6 (0.8%)	0 .	6 (0.8%)
REPRODUCTIVE FEMALE	TOTAL	6 (0.8%)	0 .	6 (0.8%)
	MENSTRUAL DISORDER	1 (0.1%)	0 .	1 (0.1%)
	PELVIC INFLAMMATION	1 (0.1%)	0 .	1 (0.1%)
	VAGINAL HEMORRHAGE	1 (0.1%)	0 .	1 (0.1%)

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PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL (N= 723)

WHO BODY SYSTEM	WHO PREFERRED TERM	Relationship		Total
		Not-Related	Related	
REPRODUCTIVE FEMALE	VAGINITIS	3 (0.4%)	0 .	3 (0.4%)
REPRODUCTIVE MALE	TOTAL	28 (3.9%)	0 .	28 (3.9%)
	BALANOPOSTHITIS	1 (0.1%)	0 .	1 (0.1%)
	IMPOTENCE	8 (1.1%)	0 .	8 (1.1%)
	ORCHITIS	1 (0.1%)	0 .	1 (0.1%)
	PENIS DISORDER	1 (0.1%)	0 .	1 (0.1%)
	PROSTATIC DISORDER	17 (2.4%)	0 .	17 (2.4%)
	TESTIS DISORDER	1 (0.1%)	0 .	1 (0.1%)
RESISTANCE MECHANISM	TOTAL	159 (22.0%)	2 (0.3%)	161 (22.3%)
	ABSCESS	6 (0.8%)	0 .	6 (0.8%)
	HERPES SIMPLEX	4 (0.6%)	0 .	4 (0.6%)
	HERPES ZOSTER	10 (1.4%)	0 .	10 (1.4%)
	INFECTION	17 (2.4%)	0 .	17 (2.4%)
	INFECTION BACTERIAL	2 (0.3%)	0 .	2 (0.3%)
	INFECTION FUNGAL	6 (0.8%)	0 .	6 (0.8%)
	INFECTION VIRAL	58 (8.0%)	2 (0.3%)	60 (8.3%)
	MONILIASIS	9 (1.2%)	0 .	9 (1.2%)
	MONILIASIS GENITAL	1 (0.1%)	0 .	1 (0.1%)
	OTITIS MEDIA	8 (1.1%)	0 .	8 (1.1%)
	SEPSIS	3 (0.4%)	0 .	3 (0.4%)
	UPPER RESP TRACT INFECTION	69 (9.5%)	2 (0.3%)	71 (9.8%)
RESPIRATORY SYSTEM	TOTAL	517 (71.5%)	14 (1.9%)	531 (73.4%)
	APNEA	2 (0.3%)	0 .	2 (0.3%)
	ASTHMA	3 (0.4%)	0 .	3 (0.4%)
	BRONCHITIS	22 (3.0%)	0 .	22 (3.0%)
	CHEST X-RAY ABNORMAL	3 (0.4%)	0 .	3 (0.4%)
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	470 (65.0%)	12 (1.7%)	482 (66.7%)
	COUGHING	42 (5.8%)	2 (0.3%)	44 (6.1%)
	DYSPNEA	21 (2.9%)	0 .	21 (2.9%)
	EPISTAXIS	4 (0.6%)	0 .	4 (0.6%)
	HEMOPTYSIS	9 (1.2%)	1 (0.1%)	10 (1.4%)
	HYPERVENTILATION	1 (0.1%)	0 .	1 (0.1%)
	HYPOXIA	2 (0.3%)	0 .	2 (0.3%)
	LARYNGITIS	5 (0.7%)	0 .	5 (0.7%)

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PROTOCOL 040

PRIOR TREATMENT: TOTAL (N= 723)

WHO BODY SYSTEM	WHO PREFERRED TERM	Relationship		Total
		Not-Related	Related	
RESPIRATORY SYSTEM	PHARYNGITIS	57 (7.9%)	0 .	57 (7.9%)
	PLEURAL EFFUSION	2 (0.3%)	0 .	2 (0.3%)
	PLEURAL PAIN	2 (0.3%)	0 .	2 (0.3%)
	PLEURISY	2 (0.3%)	0 .	2 (0.3%)
	PNEUMONIA	24 (3.3%)	0 .	24 (3.3%)
	PNEUMONIA LOBAR	1 (0.1%)	0 .	1 (0.1%)
	RESPIRATORY DISORDER	38 (5.3%)	0 .	38 (5.3%)
	RESPIRATORY INSUFFICIENCY	3 (0.4%)	0 .	3 (0.4%)
	RHINITIS	72 (10.0%)	0 .	72 (10.0%)
	SINUSITIS	30 (4.1%)	0 .	30 (4.1%)
	SPUTUM INCREASED	7 (1.0%)	0 .	7 (1.0%)
	TRACHEITIS	4 (0.6%)	0 .	4 (0.6%)
SKIN AND APPENDAGES	TOTAL	68 (9.4%)	5 (0.7%)	73 (10.1%)
	ALOPECIA	2 (0.3%)	0 .	2 (0.3%)
	ANGIOEDEMA	1 (0.1%)	0 .	1 (0.1%)
	BULLOUS ERUPTION	1 (0.1%)	0 .	1 (0.1%)
	DERMATITIS	7 (1.0%)	1 (0.1%)	8 (1.1%)
	DERMATITIS FUNGAL	2 (0.3%)	0 .	2 (0.3%)
	DERMATITIS LICHENOID	2 (0.3%)	0 .	2 (0.3%)
	ECZEMA	9 (1.2%)	0 .	9 (1.2%)
	FOLLICULITIS	2 (0.3%)	0 .	2 (0.3%)
	FURUNCULOSIS	1 (0.1%)	0 .	1 (0.1%)
	HYPERKERATOSIS	2 (0.3%)	0 .	2 (0.3%)
	MELANOSIS	1 (0.1%)	0 .	1 (0.1%)
	NAIL DISORDER	1 (0.1%)	0 .	1 (0.1%)
	PHOTOSENSITIVITY	1 (0.1%)	0 .	1 (0.1%)
	ALLERGIC REACT			
	PRURITUS	17 (2.4%)	1 (0.1%)	18 (2.5%)
	PSORIASIS	1 (0.1%)	0 .	1 (0.1%)
	RASH	8 (1.1%)	1 (0.1%)	9 (1.2%)
	RASH ERYTHEMATOUS	2 (0.3%)	0 .	2 (0.3%)
	RASH MACULO-PAPULAR	3 (0.4%)	0 .	3 (0.4%)
	RASH PUSTULAR	1 (0.1%)	0 .	1 (0.1%)
	ROSACEA	1 (0.1%)	0 .	1 (0.1%)
	SKIN DISORDER	9 (1.2%)	0 .	9 (1.2%)
	SKIN DRY	5 (0.7%)	0 .	5 (0.7%)
	SKIN HYPERTROPHY	3 (0.4%)	0 .	3 (0.4%)
	SKIN ULCERATION	4 (0.6%)	0 .	4 (0.6%)

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PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL (N= 723)

WHO BODY SYSTEM	WHO PREFERRED TERM	Relationship		
		Not-Related	Related	Total
SKIN AND APPENDAGES	URTICARIA	6 (0.8%)	2 (0.3%)	8 (1.1%)
	VERRUCA	1 (0.1%)	0 .	1 (0.1%)
SPECIAL SENSES OTHER	TOTAL	0 .	3 (0.4%)	3 (0.4%)
	TASTE PERVERSION	0 .	3 (0.4%)	3 (0.4%)
URINARY SYSTEM	TOTAL	98 (13.6%)	2 (0.3%)	100 (13.8%)
	ALBUMINURIA	17 (2.4%)	0 .	17 (2.4%)
	BLADDER CALCULUS	1 (0.1%)	0 .	1 (0.1%)
	CYSTITIS	7 (1.0%)	0 .	7 (1.0%)
	DYSURIA	8 (1.1%)	0 .	8 (1.1%)
	HEMATURIA	25 (3.5%)	1 (0.1%)	26 (3.6%)
	MICTURITION DISORDER	2 (0.3%)	0 .	2 (0.3%)
	MICTURITION FREQUENCY	5 (0.7%)	0 .	5 (0.7%)
	NOCTURIA	1 (0.1%)	0 .	1 (0.1%)
	PYELONEPHRITIS	2 (0.3%)	0 .	2 (0.3%)
	PYURIA	15 (2.1%)	1 (0.1%)	16 (2.2%)
	RENAL CALCULUS	2 (0.3%)	0 .	2 (0.3%)
	RENAL CYST	1 (0.1%)	0 .	1 (0.1%)
	RENAL FAILURE ACUTE	2 (0.3%)	0 .	2 (0.3%)
	RENAL FUNCTION ABNORMAL	3 (0.4%)	0 .	3 (0.4%)
	RENAL PAIN	3 (0.4%)	0 .	3 (0.4%)
	URINARY CASTS	1 (0.1%)	0 .	1 (0.1%)
	URINARY INCONTINENCE	2 (0.3%)	0 .	2 (0.3%)
	URINARY RETENTION	6 (0.8%)	0 .	6 (0.8%)
	URINARY TRACT INFECTION	32 (4.4%)	0 .	32 (4.4%)
	URINE ABNORMAL	1 (0.1%)	0 .	1 (0.1%)
VASCULAR EXTRACARDIAC	TOTAL	32 (4.4%)	0 .	32 (4.4%)
	ARTERIOSCLEROSIS	1 (0.1%)	0 .	1 (0.1%)
	ARTERITIS	1 (0.1%)	0 .	1 (0.1%)
	CEREBROVASCULAR DISORDER	5 (0.7%)	0 .	5 (0.7%)
	CLAUDICATION	3 (0.4%)	0 .	3 (0.4%)
	INTERMITTENT CRAMPS LEGS	4 (0.6%)	0 .	4 (0.6%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM, PREFERRED TERM AND RELATIONSHIP
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED
3. LIKELIEST RELATIONSHIP IS USED FOR EACH ADVERSE EVENT FOR EACH PATIENT
4. NOT RELATED=UNLIKELY OR NOT-RELATED TO TREATMENT, RELATED=SUSPECTED OR PROBABLY RELATED TO TREATMENT

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, BODY SYSTEM,
PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL (N= 723)

WHO BODY SYSTEM	WHO PREFERRED TERM	Relationship		Total
		Not-Related	Related	
VASCULAR EXTRACARDIAC	HEMORRHAGE NOS	1 (0.1%)	0 .	1 (0.1%)
	PERIPHERAL ISCHEMIA	3 (0.4%)	0 .	3 (0.4%)
	PHLEBITIS	1 (0.1%)	0 .	1 (0.1%)
	PHLEBITIS SUPERFICIAL	1 (0.1%)	0 .	1 (0.1%)
	THROMBOPHLEBITIS DEEP	2 (0.3%)	0 .	2 (0.3%)
	THROMBOPHLEBITIS LEG	1 (0.1%)	0 .	1 (0.1%)
	THROMBOPHLEBITIS	1 (0.1%)	0 .	1 (0.1%)
	RETINAL VEIN			
	THROMBOSIS ARTERIAL	1 (0.1%)	0 .	1 (0.1%)
	LEG			
	THROMBOSIS RETINAL	2 (0.3%)	0 .	2 (0.3%)
	ARTERY			
	VASCULAR DISORDER	4 (0.6%)	0 .	4 (0.6%)
VISION	VEIN DISORDER	2 (0.3%)	0 .	2 (0.3%)
	VEIN VARICOSE	3 (0.4%)	0 .	3 (0.4%)
	TOTAL	38 (5.3%)	0 .	38 (5.3%)
	BLEPHARITIS	3 (0.4%)	0 .	3 (0.4%)
	CATARACT	12 (1.7%)	0 .	12 (1.7%)
	CONJUNCTIVAL	1 (0.1%)	0 .	1 (0.1%)
	HEMORRHAGE			
	CONJUNCTIVITIS	15 (2.1%)	0 .	15 (2.1%)
	CORNEAL ULCERATION	1 (0.1%)	0 .	1 (0.1%)
	EYE ABNORMALITY	4 (0.6%)	0 .	4 (0.6%)
	GLAUCOMA	1 (0.1%)	0 .	1 (0.1%)
	MACULA LUTEA	1 (0.1%)	0 .	1 (0.1%)
	DEGENERATION			
	RETINAL DETACHMENT	1 (0.1%)	0 .	1 (0.1%)
	RETINAL DISORDER	2 (0.3%)	0 .	2 (0.3%)
	UVEITIS	1 (0.1%)	0 .	1 (0.1%)
	VISION ABNORMAL	3 (0.4%)	0 .	3 (0.4%)
	VISUAL FIELD DEFECT	1 (0.1%)	0 .	1 (0.1%)
	XEROPHTHALMIA	2 (0.3%)	0 .	2 (0.3%)
WHITE CELL AND RETICULOENDOTHELIAL SYSTE	TOTAL	36 (5.0%)	0 .	36 (5.0%)
	EOSINOPHILIA	2 (0.3%)	0 .	2 (0.3%)
	GRANULOCYTOPENIA	2 (0.3%)	0 .	2 (0.3%)

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4. NOT RELATED=UNLIKELY OR NOT-RELATED TO TREATMENT, RELATED=SUSPECTED OR PROBABLY RELATED TO TREATMENT

TABLE 15.3

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED RELATIONSHIP TO TREATMENT, BODY SYSTEM,
PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL (N= 723)

WHO BODY SYSTEM	WHO PREFERRED TERM	Relationship		Total
		Not-Related	Related	
WHITE CELL AND RETICULOENDOTHELIAL SYSTE	LEUKOCYTOSIS	23 (3.2%)	0 .	23 (3.2%)
	LEUKOPENIA	3 (0.4%)	0 .	3 (0.4%)
	LYMPHADENOPATHY	5 (0.7%)	0 .	5 (0.7%)
	LYMPHADENOPATHY CERVICAL	1 (0.1%)	0 .	1 (0.1%)
	LYMPHANGITIS	1 (0.1%)	0 .	1 (0.1%)
	LYMPHEDEMA	1 (0.1%)	0 .	1 (0.1%)
	LYMPHOPENIA	2 (0.3%)	0 .	2 (0.3%)

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4. NOT RELATED=UNLIKELY OR NOT-RELATED TO TREATMENT, RELATED=SUSPECTED OR PROBABLY RELATED TO TREATMENT

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: PLACEBO (N= 243)

WHO BODY SYSTEM	WHO PREFERRED TERM	Missing		Mild		Intensity Moderate		Severe		Total	
TOTAL	TOTAL	0	.	37	(15.2%)	132	(54.3%)	60	(24.7%)	229	(94.2%)
APPLICATION SITE	TOTAL	0	.	2	(0.8%)	1	(0.4%)	0	.	3	(1.2%)
	OTITIS EXTERNA	0	.	2	(0.8%)	1	(0.4%)	0	.	3	(1.2%)
AUTONOMIC NERVOUS SYSTEM	TOTAL	0	.	2	(0.8%)	2	(0.8%)	1	(0.4%)	5	(2.1%)
	MOUTH DRY	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	SWEATING INCREASED	0	.	1	(0.4%)	2	(0.8%)	1	(0.4%)	4	(1.6%)
BODY AS A WHOLE GENERAL	TOTAL	0	.	33	(13.6%)	36	(14.8%)	5	(2.1%)	74	(30.5%)
	ALCOHOL INTOLERANCE	0	.	0	.	0	.	1	(0.4%)	1	(0.4%)
	ALLERGIC REACTION	0	.	1	(0.4%)	1	(0.4%)	0	.	2	(0.8%)
	ASTHENIA	0	.	4	(1.6%)	3	(1.2%)	1	(0.4%)	8	(3.3%)
	CELLULITIS	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	CHEST PAIN	0	.	9	(3.7%)	4	(1.6%)	2	(0.8%)	15	(6.2%)
	CHEST PAIN PRECORDIAL	0	.	3	(1.2%)	1	(0.4%)	0	.	4	(1.6%)
	CHEST PAIN SUBSTERNAL	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	EDEMA DEPENDENT	0	.	3	(1.2%)	0	.	0	.	3	(1.2%)
	EDEMA LEGS	0	.	5	(2.1%)	0	.	0	.	5	(2.1%)
	FATIGUE	0	.	4	(1.6%)	4	(1.6%)	0	.	8	(3.3%)
	FEVER	0	.	9	(3.7%)	1	(0.4%)	1	(0.4%)	11	(4.5%)
	HOT FLUSHES	0	.	0	.	1	(0.4%)	0	.	1	(0.4%)
	INFLUENZA-LIKE SYMPTOMS	0	.	0	.	1	(0.4%)	0	.	1	(0.4%)
	INJURY	0	.	6	(2.5%)	19	(7.8%)	1	(0.4%)	26	(10.7%)
	MALAISE	0	.	8	(3.3%)	2	(0.8%)	0	.	10	(4.1%)
	PAIN	0	.	4	(1.6%)	5	(2.1%)	0	.	9	(3.7%)
	RIGORS	0	.	0	.	1	(0.4%)	0	.	1	(0.4%)
CARDIOVASCULAR GENERAL	TOTAL	0	.	10	(4.1%)	12	(4.9%)	2	(0.8%)	24	(9.9%)
	ANEURYSM	0	.	0	.	1	(0.4%)	0	.	1	(0.4%)
	CARDIAC FAILURE	0	.	0	.	1	(0.4%)	1	(0.4%)	2	(0.8%)
	CARDIOMEGALY	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	ECG ABNORMAL	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	ECG ABNORMAL SPECIFIC	0	.	0	.	1	(0.4%)	0	.	1	(0.4%)
	HEART VALVE DISORDERS	0	.	0	.	1	(0.4%)	0	.	1	(0.4%)
	HYPERTENSION	0	.	7	(2.9%)	3	(1.2%)	0	.	10	(4.1%)

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TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: PLACEBO (N= 243)

WHO BODY SYSTEM	WHO PREFERRED TERM	Missing		Mild		Intensity Moderate		Severe		Total	
CARDIOVASCULAR GENERAL	HYPERTENSION	0	.	0	.	3	(1.2%)	0	.	3	(1.2%)
	AGGRAVATED										
	HYPOTENSION	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	HYPOTENSION POSTURAL	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	SYNCOPE	0	.	0	.	3	(1.2%)	1	(0.4%)	4	(1.6%)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	TOTAL	0	.	27	(11.1%)	29	(11.9%)	2	(0.8%)	58	(23.9%)
	ATAXIA	0	.	0	.	1	(0.4%)	0	.	1	(0.4%)
	DIZZINESS	0	.	5	(2.1%)	4	(1.6%)	0	.	9	(3.7%)
	DYSPHONIA	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	EXTRAPYRAMIDAL DISORDER	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	HEADACHE	0	.	14	(5.8%)	17	(7.0%)	1	(0.4%)	32	(13.2%)
	HYPERTONIA	0	.	0	.	1	(0.4%)	0	.	1	(0.4%)
	HYPESTHESIA	0	.	0	.	1	(0.4%)	0	.	1	(0.4%)
	MIGRAINE	0	.	1	(0.4%)	1	(0.4%)	0	.	2	(0.8%)
	MUSCLE CONTRACTIONS INVOLUNTARY	0	.	0	.	1	(0.4%)	0	.	1	(0.4%)
	NEURALGIA	0	.	3	(1.2%)	4	(1.6%)	0	.	7	(2.9%)
	PARESIS	0	.	2	(0.8%)	0	.	0	.	2	(0.8%)
	PARESTHESIA	0	.	1	(0.4%)	1	(0.4%)	0	.	2	(0.8%)
	TREMOR	0	.	3	(1.2%)	0	.	0	.	3	(1.2%)
	TRIGEMINAL NEURALGIA	0	.	0	.	0	.	1	(0.4%)	1	(0.4%)
	VERTIGO	0	.	2	(0.8%)	3	(1.2%)	0	.	5	(2.1%)
ENDOCRINE	TOTAL	0	.	2	(0.8%)	1	(0.4%)	1	(0.4%)	4	(1.6%)
	GOITRE	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	HYPERTHYROIDISM	0	.	0	.	0	.	1	(0.4%)	1	(0.4%)
	MASTITIS MALE	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	SIALOADENITIS	0	.	0	.	1	(0.4%)	0	.	1	(0.4%)
	THYROIDITIS	0	.	0	.	1	(0.4%)	0	.	1	(0.4%)
GASTROINTESTINAL SYSTEM	TOTAL	0	.	62	(25.5%)	64	(26.3%)	8	(3.3%)	134	(55.1%)
	ABDOMINAL PAIN	0	.	22	(9.1%)	24	(9.9%)	4	(1.6%)	50	(20.6%)
	ANOREXIA	0	.	4	(1.6%)	3	(1.2%)	0	.	7	(2.9%)
	APPETITE INCREASED	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	CONSTIPATION	0	.	3	(1.2%)	2	(0.8%)	0	.	5	(2.1%)
	DIARRHEA	0	.	24	(9.9%)	18	(7.4%)	2	(0.8%)	44	(18.1%)

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TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: PLACEBO (N= 243)

WHO BODY SYSTEM	WHO PREFERRED TERM	Missing		Mild		Intensity Moderate		Severe		Total	
GASTROINTESTINAL SYSTEM	DUODENITIS	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	DYSPEPSIA	0	.	21	(8.6%)	7	(2.9%)	2	(0.8%)	30	(12.3%)
	ENTERITIS	0	.	2	(0.8%)	0	.	0	.	2	(0.8%)
	ESOPHAGITIS	0	.	1	(0.4%)	2	(0.8%)	0	.	3	(1.2%)
	ESOPHAGOSPASM	0	.	0	.	1	(0.4%)	0	.	1	(0.4%)
	FLATULENCE	0	.	4	(1.6%)	1	(0.4%)	0	.	5	(2.1%)
	GASTRITIS	0	.	3	(1.2%)	3	(1.2%)	0	.	6	(2.5%)
	GASTROENTERITIS	0	.	3	(1.2%)	8	(3.3%)	0	.	11	(4.5%)
	GASTROESOPHAGEAL REFLUX	0	.	2	(0.8%)	1	(0.4%)	0	.	3	(1.2%)
	GASTROINTESTINAL DISORDER NOS	0	.	3	(1.2%)	2	(0.8%)	0	.	5	(2.1%)
	GI HEMORRHAGE	0	.	0	.	2	(0.8%)	1	(0.4%)	3	(1.2%)
	HEMORRHAGE RECTUM	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	HEMORRHOIDS	0	.	2	(0.8%)	0	.	0	.	2	(0.8%)
	INTESTINAL OBSTRUCTION	0	.	0	.	1	(0.4%)	0	.	1	(0.4%)
	IRRITABLE BOWEL SYNDROME	1	(0.4%)	0	.	0	.	0	.	1	(0.4%)
	MELENA	0	.	2	(0.8%)	3	(1.2%)	0	.	5	(2.1%)
	NAUSEA	0	.	24	(9.9%)	10	(4.1%)	0	.	34	(14.0%)
	PANCREATITIS	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	PERIODONTITIS	0	.	2	(0.8%)	2	(0.8%)	1	(0.4%)	5	(2.1%)
	PROCTITIS	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	STOMATITIS	0	.	0	.	1	(0.4%)	0	.	1	(0.4%)
	TOOTH ACHE	0	.	2	(0.8%)	0	.	0	.	2	(0.8%)
	TOOTH CARIES	0	.	2	(0.8%)	0	.	0	.	2	(0.8%)
	TOOTH DISORDER	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	VOMITING	0	.	8	(3.3%)	6	(2.5%)	1	(0.4%)	15	(6.2%)
HEARING AND VESTIBULAR	TOTAL	0	.	5	(2.1%)	3	(1.2%)	0	.	8	(3.3%)
	DEAFNESS	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	EAR DISORDER NOS	0	.	1	(0.4%)	2	(0.8%)	0	.	3	(1.2%)
	EARACHE	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	TINNITUS	0	.	2	(0.8%)	0	.	0	.	2	(0.8%)
	VESTIBULAR DISORDER	0	.	0	.	1	(0.4%)	0	.	1	(0.4%)
HEART RATE AND RHYTHM	TOTAL	0	.	22	(9.1%)	7	(2.9%)	2	(0.8%)	31	(12.8%)
	ARRHYTHMIA	0	.	2	(0.8%)	1	(0.4%)	1	(0.4%)	4	(1.6%)

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TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: PLACEBO (N= 243)

WHO BODY SYSTEM	WHO PREFERRED TERM	Missing		Mild		Intensity Moderate		Severe		Total	
HEART RATE AND RHYTHM	ARRHYTHMIA ATRIAL	0	.	0	.	0	.	1	(0.4%)	1	(0.4%)
	BRADYCARDIA	0	.	7	(2.9%)	0	.	0	.	7	(2.9%)
	BUNDLE BRANCH BLOCK	0	.	2	(0.8%)	0	.	0	.	2	(0.8%)
	EXTRASYSTOLES	0	.	4	(1.6%)	0	.	0	.	4	(1.6%)
	EXTRASYSTOLES SUPRAVENTRICULAR	0	.	4	(1.6%)	1	(0.4%)	0	.	5	(2.1%)
	FIBRILLATION ATRIAL	0	.	1	(0.4%)	2	(0.8%)	0	.	3	(1.2%)
	QT INCREASED	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	TACHYCARDIA	0	.	7	(2.9%)	3	(1.2%)	0	.	10	(4.1%)
LIVER AND BILIARY SYSTEM	TOTAL	0	.	8	(3.3%)	4	(1.6%)	1	(0.4%)	13	(5.3%)
	BILIRUBINEMIA	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	CHOLELITHIASIS	0	.	2	(0.8%)	0	.	0	.	2	(0.8%)
	GAMMA-GT INCREASED	0	.	4	(1.6%)	2	(0.8%)	1	(0.4%)	7	(2.9%)
	HEPATIC CIRRHOSIS	0	.	0	.	1	(0.4%)	0	.	1	(0.4%)
	HEPATIC ENZYMES INCREASED	0	.	3	(1.2%)	0	.	0	.	3	(1.2%)
	HEPATITIS INFECTIOUS	0	.	0	.	1	(0.4%)	0	.	1	(0.4%)
	SGPT INCREASED	0	.	0	.	1	(0.4%)	0	.	1	(0.4%)
METABOLIC AND NUTRITIONAL	TOTAL	0	.	21	(8.6%)	15	(6.2%)	0	.	36	(14.8%)
	DIABETES MELLITUS	0	.	2	(0.8%)	0	.	0	.	2	(0.8%)
	GLYCOSURIA	0	.	3	(1.2%)	1	(0.4%)	0	.	4	(1.6%)
	GOUT	0	.	1	(0.4%)	4	(1.6%)	0	.	5	(2.1%)
	HYPERCHOLESTEROLEMIA	0	.	4	(1.6%)	0	.	0	.	4	(1.6%)
	HYPERGLYCEMIA	0	.	6	(2.5%)	2	(0.8%)	0	.	8	(3.3%)
	HYPERKALEMIA	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	HYPERNATREMIA	0	.	0	.	1	(0.4%)	0	.	1	(0.4%)
	HYPERTRIGLYCERIDEMIA	0	.	0	.	1	(0.4%)	0	.	1	(0.4%)
	HYPERURICEMIA	0	.	3	(1.2%)	0	.	0	.	3	(1.2%)
	HYPOCHLOREMIA	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	HYPOGLYCEMIA	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	HYPOKALEMIA	0	.	1	(0.4%)	1	(0.4%)	0	.	2	(0.8%)
	HYPONATREMIA	0	.	2	(0.8%)	0	.	0	.	2	(0.8%)
	OBESITY	0	.	0	.	1	(0.4%)	0	.	1	(0.4%)
	WEIGHT DECREASE	0	.	2	(0.8%)	7	(2.9%)	0	.	9	(3.7%)
	WEIGHT INCREASE	0	.	0	.	1	(0.4%)	0	.	1	(0.4%)

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TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: PLACEBO (N= 243)

WHO BODY SYSTEM	WHO PREFERRED TERM	Missing		Mild		Intensity Moderate		Severe		Total	
MUSCULOSKELETAL SYSTEM	TOTAL	0	.	22	(9.1%)	34	(14.0%)	4	(1.6%)	60	(24.7%)
	ARTHRALGIA	0	.	4	(1.6%)	16	(6.6%)	0	.	20	(8.2%)
	ARTHRITIS	0	.	4	(1.6%)	2	(0.8%)	1	(0.4%)	7	(2.9%)
	ARTHRITIS AGGRAVATED	0	.	1	(0.4%)	1	(0.4%)	0	.	2	(0.8%)
	ARTHROPATHY	0	.	2	(0.8%)	0	.	0	.	2	(0.8%)
	ARTHROSIS	0	.	1	(0.4%)	1	(0.4%)	0	.	2	(0.8%)
	BACK PAIN	0	.	9	(3.7%)	14	(5.8%)	0	.	23	(9.5%)
	MYALGIA	0	.	6	(2.5%)	6	(2.5%)	1	(0.4%)	13	(5.3%)
	MYOSITIS	0	.	0	.	1	(0.4%)	0	.	1	(0.4%)
	OSTEONECROSIS	0	.	0	.	0	.	1	(0.4%)	1	(0.4%)
	OSTEOPOROSIS	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	SKELETAL PAIN	0	.	1	(0.4%)	1	(0.4%)	0	.	2	(0.8%)
	TENDON DISORDER	0	.	0	.	0	.	1	(0.4%)	1	(0.4%)
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	TOTAL	0	.	2	(0.8%)	4	(1.6%)	3	(1.2%)	9	(3.7%)
	ANGINA PECTORIS	0	.	2	(0.8%)	3	(1.2%)	2	(0.8%)	7	(2.9%)
	AORTIC STENOSIS	0	.	0	.	1	(0.4%)	0	.	1	(0.4%)
	MYOCARDIAL INFARCTION	0	.	0	.	0	.	1	(0.4%)	1	(0.4%)
NEOPLASM	TOTAL	0	.	5	(2.1%)	7	(2.9%)	11	(4.5%)	23	(9.5%)
	ADENOCARCINOMA NOS	0	.	0	.	0	.	1	(0.4%)	1	(0.4%)
	BASAL CELL CARCINOMA	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	BLADDER CARCINOMA	0	.	0	.	0	.	2	(0.8%)	2	(0.8%)
	CARCINOMA	0	.	0	.	2	(0.8%)	1	(0.4%)	3	(1.2%)
	COLON CARCINOMA	0	.	0	.	0	.	1	(0.4%)	1	(0.4%)
	GASTRIC CARCINOMA	0	.	0	.	0	.	1	(0.4%)	1	(0.4%)
	LIPOMA	0	.	2	(0.8%)	0	.	0	.	2	(0.8%)
	LYMPHOMA MALIGNANT	0	.	0	.	0	.	1	(0.4%)	1	(0.4%)
	NEOPLASM MALIGNANT	0	.	0	.	0	.	1	(0.4%)	1	(0.4%)
	NEOPLASM NOS	0	.	3	(1.2%)	5	(2.1%)	2	(0.8%)	10	(4.1%)
	PULMONARY CARCINOMA	0	.	0	.	0	.	1	(0.4%)	1	(0.4%)
PLATELET BLEEDING AND CLOTTING	TOTAL	0	.	0	.	1	(0.4%)	0	.	1	(0.4%)
	PURPURA	0	.	0	.	1	(0.4%)	0	.	1	(0.4%)
PSYCHIATRIC	TOTAL	0	.	16	(6.6%)	19	(7.8%)	0	.	35	(14.4%)
	AGITATION	0	.	0	.	2	(0.8%)	0	.	2	(0.8%)

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TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: PLACEBO (N= 243)

WHO BODY SYSTEM	WHO PREFERRED TERM	Intensity					Total
		Missing	Mild	Moderate	Severe		
PSYCHIATRIC	ANXIETY	0 .	7 (2.9%)	6 (2.5%)	0 .		13 (5.3%)
	APATHY	0 .	1 (0.4%)	0 .	0 .		1 (0.4%)
	CONCENTRATION IMPAIRED	0 .	0 .	1 (0.4%)	0 .		1 (0.4%)
	DEPRESSION	0 .	3 (1.2%)	7 (2.9%)	0 .		10 (4.1%)
	INSOMNIA	0 .	4 (1.6%)	4 (1.6%)	0 .		8 (3.3%)
	NERVOUSNESS	0 .	3 (1.2%)	2 (0.8%)	0 .		5 (2.1%)
	SOMNOLENCE	0 .	1 (0.4%)	3 (1.2%)	0 .		4 (1.6%)
RED BLOOD CELL	TOTAL	0 .	2 (0.8%)	1 (0.4%)	0 .		3 (1.2%)
	ANEMIA	0 .	1 (0.4%)	1 (0.4%)	0 .		2 (0.8%)
	ANEMIA MACROCYTIC	0 .	1 (0.4%)	0 .	0 .		1 (0.4%)
REPRODUCTIVE FEMALE	TOTAL	0 .	0 .	1 (0.4%)	0 .		1 (0.4%)
	PELVIC INFLAMMATION	0 .	0 .	1 (0.4%)	0 .		1 (0.4%)
REPRODUCTIVE MALE	TOTAL	0 .	8 (3.3%)	7 (2.9%)	0 .		15 (6.2%)
	BALANOPOSTHITIS	0 .	1 (0.4%)	0 .	0 .		1 (0.4%)
	IMPOTENCE	0 .	1 (0.4%)	1 (0.4%)	0 .		2 (0.8%)
	ORCHITIS	0 .	0 .	1 (0.4%)	0 .		1 (0.4%)
	PENIS DISORDER	0 .	1 (0.4%)	0 .	0 .		1 (0.4%)
	PROSTATIC DISORDER	0 .	6 (2.5%)	5 (2.1%)	0 .		11 (4.5%)
RESISTANCE MECHANISM	TOTAL	0 .	22 (9.1%)	27 (11.1%)	1 (0.4%)		50 (20.6%)
	ABSCCESS	0 .	1 (0.4%)	1 (0.4%)	0 .		2 (0.8%)
	HERPES SIMPLEX	0 .	0 .	1 (0.4%)	0 .		1 (0.4%)
	HERPES ZOSTER	0 .	0 .	2 (0.8%)	0 .		2 (0.8%)
	INFECTION	0 .	3 (1.2%)	3 (1.2%)	0 .		6 (2.5%)
	INFECTION FUNGAL	0 .	4 (1.6%)	0 .	0 .		4 (1.6%)
	INFECTION VIRAL	0 .	9 (3.7%)	12 (4.9%)	0 .		21 (8.6%)
	MONILIASIS	0 .	2 (0.8%)	1 (0.4%)	0 .		3 (1.2%)
	OTITIS MEDIA	0 .	1 (0.4%)	2 (0.8%)	0 .		3 (1.2%)
	SEPSIS	0 .	0 .	0 .	1 (0.4%)		1 (0.4%)
	UPPER RESP TRACT INFECTION	0 .	11 (4.5%)	9 (3.7%)	0 .		20 (8.2%)
RESPIRATORY SYSTEM	TOTAL	0 .	41 (16.9%)	105 (43.2%)	28 (11.5%)		174 (71.6%)
	APNEA	0 .	0 .	1 (0.4%)	0 .		1 (0.4%)
	ASTHMA	0 .	1 (0.4%)	1 (0.4%)	0 .		2 (0.8%)
	BRONCHITIS	0 .	2 (0.8%)	6 (2.5%)	0 .		8 (3.3%)

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TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: PLACEBO (N= 243)

WHO BODY SYSTEM	WHO PREFERRED TERM	Missing		Mild		Intensity Moderate		Severe		Total	
RESPIRATORY SYSTEM	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	0	.	35	(14.4%)	97	(39.9%)	23	(9.5%)	155	(63.8%)
	COUGHING	0	.	10	(4.1%)	3	(1.2%)	0	.	13	(5.3%)
	DYSPNEA	0	.	4	(1.6%)	4	(1.6%)	0	.	8	(3.3%)
	EPISTAXIS	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	HEMOPTYSIS	0	.	3	(1.2%)	0	.	0	.	3	(1.2%)
	HYPERVENTILATION	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	HYPOXIA	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	LARYNGITIS	0	.	2	(0.8%)	1	(0.4%)	0	.	3	(1.2%)
	PHARYNGITIS	0	.	8	(3.3%)	7	(2.9%)	0	.	15	(6.2%)
	PLEURAL EFFUSION	0	.	0	.	1	(0.4%)	0	.	1	(0.4%)
	PNEUMONIA	0	.	0	.	6	(2.5%)	4	(1.6%)	10	(4.1%)
	RESPIRATORY DISORDER	0	.	5	(2.1%)	4	(1.6%)	1	(0.4%)	10	(4.1%)
	RHINITIS	0	.	22	(9.1%)	6	(2.5%)	0	.	28	(11.5%)
	SINUSITIS	0	.	5	(2.1%)	9	(3.7%)	0	.	14	(5.8%)
	SPUTUM INCREASED	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	TRACHEITIS	0	.	0	.	0	.	1	(0.4%)	1	(0.4%)
SKIN AND APPENDAGES	TOTAL	0	.	18	(7.4%)	7	(2.9%)	1	(0.4%)	26	(10.7%)
	DERMATITIS	0	.	1	(0.4%)	1	(0.4%)	0	.	2	(0.8%)
	DERMATITIS FUNGAL	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	ECZEMA	0	.	3	(1.2%)	1	(0.4%)	0	.	4	(1.6%)
	FURUNCULOSIS	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	HYPERKERATOSIS	0	.	0	.	1	(0.4%)	0	.	1	(0.4%)
	NAIL DISORDER	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	PHOTOSENSITIVITY	0	.	0	.	1	(0.4%)	0	.	1	(0.4%)
	ALLERGIC REACT										
	PRURITUS	0	.	3	(1.2%)	1	(0.4%)	0	.	4	(1.6%)
	RASH	0	.	3	(1.2%)	1	(0.4%)	0	.	4	(1.6%)
	RASH ERYTHEMATOUS	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
	ROSACEA	0	.	0	.	1	(0.4%)	0	.	1	(0.4%)
	SKIN DISORDER	0	.	1	(0.4%)	2	(0.8%)	1	(0.4%)	4	(1.6%)
	SKIN DRY	0	.	3	(1.2%)	0	.	0	.	3	(1.2%)
	SKIN HYPERTROPHY	0	.	1	(0.4%)	1	(0.4%)	0	.	2	(0.8%)
	URTICARIA	0	.	0	.	1	(0.4%)	0	.	1	(0.4%)
	VERRUCA	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
SPECIAL SENSES	TOTAL	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)
OTHER											
	TASTE PERVERSION	0	.	1	(0.4%)	0	.	0	.	1	(0.4%)

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INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, PREFERRED TERM AND
PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: PLACEBO (N= 243)

WHO BODY SYSTEM	WHO PREFERRED TERM	Intensity					Total
		Missing	Mild	Moderate	Severe		
URINARY SYSTEM	TOTAL	0	21 (8.6%)	12 (4.9%)	2 (0.8%)		35 (14.4%)
	ALBUMINURIA	0	5 (2.1%)	0	0		5 (2.1%)
	CYSTITIS	0	0	2 (0.8%)	0		2 (0.8%)
	DYSURIA	0	3 (1.2%)	1 (0.4%)	1 (0.4%)		5 (2.1%)
	HEMATURIA	0	9 (3.7%)	3 (1.2%)	1 (0.4%)		13 (5.3%)
	MICTURITION DISORDER	0	1 (0.4%)	0	0		1 (0.4%)
	MICTURITION FREQUENCY	0	1 (0.4%)	1 (0.4%)	0		2 (0.8%)
	PYURIA	0	3 (1.2%)	1 (0.4%)	0		4 (1.6%)
	RENAL CALCULUS	0	1 (0.4%)	0	0		1 (0.4%)
	RENAL FUNCTION ABNORMAL	0	2 (0.8%)	0	0		2 (0.8%)
	URINARY CASTS	0	1 (0.4%)	0	0		1 (0.4%)
	URINARY RETENTION	0	0	2 (0.8%)	0		2 (0.8%)
	URINARY TRACT INFECTION	0	5 (2.1%)	4 (1.6%)	1 (0.4%)		10 (4.1%)
VASCULAR EXTRACARDIAC	TOTAL	0	6 (2.5%)	5 (2.1%)	1 (0.4%)		12 (4.9%)
	ARTERITIS	0	0	1 (0.4%)	0		1 (0.4%)
	CEREBROVASCULAR DISORDER	0	1 (0.4%)	0	0		1 (0.4%)
	CLAUDICATION	0	1 (0.4%)	1 (0.4%)	0		2 (0.8%)
	INTERMITTENT CRAMPS LEGS	0	2 (0.8%)	0	0		2 (0.8%)
	HEMORRHAGE NOS	0	0	1 (0.4%)	0		1 (0.4%)
	PERIPHERAL ISCHEMIA	0	2 (0.8%)	0	0		2 (0.8%)
	THROMBOPHLEBITIS DEEP	0	0	1 (0.4%)	1 (0.4%)		2 (0.8%)
	VASCULAR DISORDER	0	0	1 (0.4%)	0		1 (0.4%)
	VEIN DISORDER	0	1 (0.4%)	0	0		1 (0.4%)
VISION	TOTAL	0	7 (2.9%)	8 (3.3%)	2 (0.8%)		17 (7.0%)
	BLEPHARITIS	0	2 (0.8%)	0	0		2 (0.8%)
	CATARACT	0	3 (1.2%)	2 (0.8%)	1 (0.4%)		6 (2.5%)
	CONJUNCTIVITIS	0	5 (2.1%)	2 (0.8%)	0		7 (2.9%)
	EYE ABNORMALITY	0	1 (0.4%)	1 (0.4%)	0		2 (0.8%)
	MACULA LUTEA DEGENERATION	0	0	1 (0.4%)	0		1 (0.4%)
	RETINAL DETACHMENT	0	0	0	1 (0.4%)		1 (0.4%)
	RETINAL DISORDER	0	1 (0.4%)	1 (0.4%)	0		2 (0.8%)
	VISION ABNORMAL	0	1 (0.4%)	1 (0.4%)	0		2 (0.8%)
	XEROPHTHALMIA	0	2 (0.8%)	0	0		2 (0.8%)

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TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, PREFERRED TERM AND
PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: PLACEBO (N= 243)

WHO BODY SYSTEM	WHO PREFERRED TERM	Intensity					Total	
		Missing		Mild	Moderate	Severe		
WHITE CELL AND RETICULOENDOTHELIAL SYSTE	TOTAL	0	.	7 (2.9%)	6 (2.5%)	0	.	13 (5.3%)
	LEUKOCYTOSIS	0	.	4 (1.6%)	2 (0.8%)	0	.	6 (2.5%)
	LEUKOPENIA	0	.	1 (0.4%)	0	0	.	1 (0.4%)
	LYMPHADENOPATHY	0	.	1 (0.4%)	2 (0.8%)	0	.	3 (1.2%)
	LYMPHANGITIS	0	.	0	1 (0.4%)	0	.	1 (0.4%)
	LYMPHEDEMA	0	.	1 (0.4%)	0	0	.	1 (0.4%)
	LYMPHOPENIA	0	.	0	1 (0.4%)	0	.	1 (0.4%)

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INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499 (N= 480)

WHO BODY SYSTEM	WHO PREFERRED TERM	Missing		Mild		Intensity Moderate		Severe		Total	
TOTAL	TOTAL	0	.	71	(14.8%)	258	(53.8%)	117	(24.4%)	446	(92.9%)
APPLICATION SITE	TOTAL	0	.	2	(0.4%)	2	(0.4%)	1	(0.2%)	5	(1.0%)
	INJECTION SITE	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	INFLAMMATION										
	OTITIS EXTERNA	0	.	2	(0.4%)	2	(0.4%)	1	(0.2%)	5	(1.0%)
	TYMPANIC MEMBRANE PERFORATION	0	.	1	(0.2%)	0	.	0	.	1	(0.2%)
AUTONOMIC NERVOUS SYSTEM	TOTAL	0	.	1	(0.2%)	1	(0.2%)	0	.	2	(0.4%)
	MOUTH DRY	0	.	1	(0.2%)	1	(0.2%)	0	.	2	(0.4%)
BODY AS A WHOLE GENERAL	TOTAL	0	.	48	(10.0%)	69	(14.4%)	13	(2.7%)	130	(27.1%)
	ALLERGIC REACTION	0	.	1	(0.2%)	1	(0.2%)	0	.	2	(0.4%)
	ASTHENIA	0	.	8	(1.7%)	6	(1.3%)	1	(0.2%)	15	(3.1%)
	CELLULITIS	0	.	1	(0.2%)	2	(0.4%)	1	(0.2%)	4	(0.8%)
	CHEST PAIN	0	.	9	(1.9%)	15	(3.1%)	2	(0.4%)	26	(5.4%)
	CHEST PAIN PRECORDIAL	0	.	2	(0.4%)	0	.	0	.	2	(0.4%)
	CHEST PAIN SUBSTERNAL	0	.	1	(0.2%)	0	.	0	.	1	(0.2%)
	DRUG LEVEL INCREASED	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	EDEMA	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	EDEMA DEPENDENT	0	.	4	(0.8%)	0	.	0	.	4	(0.8%)
	EDEMA LEGS	0	.	4	(0.8%)	1	(0.2%)	0	.	5	(1.0%)
	FACE EDEMA	0	.	1	(0.2%)	0	.	0	.	1	(0.2%)
	FATIGUE	0	.	4	(0.8%)	5	(1.0%)	0	.	9	(1.9%)
	FEVER	0	.	7	(1.5%)	1	(0.2%)	0	.	8	(1.7%)
	INFLUENZA-LIKE SYMPTOMS	0	.	0	.	3	(0.6%)	0	.	3	(0.6%)
	INJURY	0	.	22	(4.6%)	30	(6.3%)	10	(2.1%)	62	(12.9%)
	MALAISE	0	.	4	(0.8%)	2	(0.4%)	0	.	6	(1.3%)
	PAIN	0	.	11	(2.3%)	11	(2.3%)	0	.	22	(4.6%)
	RIGORS	0	.	1	(0.2%)	0	.	0	.	1	(0.2%)
	THERAPEUTIC RESPONSE INCREASED	0	.	1	(0.2%)	2	(0.4%)	0	.	3	(0.6%)
CARDIOVASCULAR GENERAL	TOTAL	0	.	25	(5.2%)	27	(5.6%)	5	(1.0%)	57	(11.9%)
	ANEURYSM	0	.	0	.	0	.	2	(0.4%)	2	(0.4%)
	CARDIAC FAILURE	0	.	1	(0.2%)	2	(0.4%)	0	.	3	(0.6%)

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INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499 (N= 480)

WHO BODY SYSTEM	WHO PREFERRED TERM	Missing		Mild		Intensity Moderate		Severe		Total	
CARDIOVASCULAR GENERAL	CARDIOMEGALY	0	.	1	(0.2%)	1	(0.2%)	0	.	2	(0.4%)
	COR PULMONALE	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	CYANOSIS	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	ECG ABNORMAL	0	.	2	(0.4%)	0	.	0	.	2	(0.4%)
	ECG ABNORMAL SPECIFIC	0	.	1	(0.2%)	1	(0.2%)	0	.	2	(0.4%)
	HYPERTENSION	0	.	19	(4.0%)	12	(2.5%)	1	(0.2%)	32	(6.7%)
	HYPERTENSION AGGRAVATED	0	.	1	(0.2%)	3	(0.6%)	1	(0.2%)	5	(1.0%)
	HYPERTENSION PULMONARY	0	.	0	.	0	.	1	(0.2%)	1	(0.2%)
	HYPOTENSION	0	.	3	(0.6%)	2	(0.4%)	0	.	5	(1.0%)
	HYPOTENSION POSTURAL	0	.	3	(0.6%)	1	(0.2%)	0	.	4	(0.8%)
	SYNCOPE	0	.	4	(0.8%)	4	(0.8%)	0	.	8	(1.7%)
	TOTAL	0	.	51	(10.6%)	38	(7.9%)	6	(1.3%)	95	(19.8%)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	COMA	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	CONVULSIONS	0	.	0	.	1	(0.2%)	1	(0.2%)	2	(0.4%)
	DIZZINESS	0	.	12	(2.5%)	12	(2.5%)	1	(0.2%)	25	(5.2%)
	DYSPHONIA	0	.	4	(0.8%)	0	.	0	.	4	(0.8%)
	EXTRAPYRAMIDAL DISORDER	0	.	1	(0.2%)	0	.	0	.	1	(0.2%)
	HEADACHE	0	.	33	(6.9%)	13	(2.7%)	1	(0.2%)	47	(9.8%)
	HYPERTONIA	0	.	2	(0.4%)	1	(0.2%)	0	.	3	(0.6%)
	MIGRAINE	0	.	0	.	2	(0.4%)	0	.	2	(0.4%)
	MUSCLE CONTRACTIONS INVOLUNTARY	0	.	2	(0.4%)	0	.	0	.	2	(0.4%)
	NERVE ROOT LESION	0	.	1	(0.2%)	0	.	0	.	1	(0.2%)
	NEURALGIA	0	.	1	(0.2%)	8	(1.7%)	2	(0.4%)	11	(2.3%)
	NEUROPATHY	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	NEUROPATHY PERIPHERAL	0	.	0	.	2	(0.4%)	0	.	2	(0.4%)
	PARESIS	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	PARESTHESIA	0	.	2	(0.4%)	0	.	0	.	2	(0.4%)
	PARKINSONISM	0	.	0	.	0	.	1	(0.2%)	1	(0.2%)
	AGGRAVATED TREMOR	0	.	1	(0.2%)	2	(0.4%)	0	.	3	(0.6%)
	VERTIGO	0	.	7	(1.5%)	5	(1.0%)	1	(0.2%)	13	(2.7%)
	WITHDRAWAL HEADACHE	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	TOTAL	0	.	0	.	3	(0.6%)	0	.	3	(0.6%)
COLLAGEN	TOTAL	0	.	0	.	3	(0.6%)	0	.	3	(0.6%)

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TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499 (N= 480)

WHO BODY SYSTEM	WHO PREFERRED TERM	Missing		Mild		Intensity Moderate		Severe		Total	
COLLAGEN	ARTHRITIS RHEUMATOID	0	.	0	.	2	(0.4%)	0	.	2	(0.4%)
	ARTHRITIS RHEUMATOID AGGRAVATED	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
ENDOCRINE	TOTAL	0	.	6	(1.3%)	3	(0.6%)	0	.	9	(1.9%)
	GOITRE	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	HYPERTHYROIDISM	0	.	5	(1.0%)	1	(0.2%)	0	.	6	(1.3%)
	HYPOTHYROIDISM	0	.	2	(0.4%)	1	(0.2%)	0	.	3	(0.6%)
FETAL	TOTAL	0	.	1	(0.2%)	0	.	0	.	1	(0.2%)
	SPINE MALFORMATION	0	.	1	(0.2%)	0	.	0	.	1	(0.2%)
GASTROINTESTINAL SYSTEM	TOTAL	0	.	115	(24.0%)	63	(13.1%)	18	(3.8%)	196	(40.8%)
	ABDOMINAL PAIN	0	.	41	(8.5%)	18	(3.8%)	4	(0.8%)	63	(13.1%)
	ANOREXIA	0	.	1	(0.2%)	2	(0.4%)	0	.	3	(0.6%)
	ANUS DISORDER	0	.	2	(0.4%)	1	(0.2%)	0	.	3	(0.6%)
	COLITIS	0	.	2	(0.4%)	0	.	0	.	2	(0.4%)
	CONSTIPATION	0	.	10	(2.1%)	5	(1.0%)	0	.	15	(3.1%)
	DIARRHEA	0	.	33	(6.9%)	18	(3.8%)	0	.	51	(10.6%)
	DIARRHEA BLOODY	0	.	1	(0.2%)	0	.	0	.	1	(0.2%)
	DIVERTICULITIS	0	.	2	(0.4%)	0	.	0	.	2	(0.4%)
	DUODENAL ULCER	0	.	0	.	0	.	1	(0.2%)	1	(0.2%)
	DUODENITIS	0	.	1	(0.2%)	0	.	1	(0.2%)	2	(0.4%)
	DYSPEPSIA	0	.	23	(4.8%)	11	(2.3%)	1	(0.2%)	35	(7.3%)
	DYSPHAGIA	0	.	3	(0.6%)	1	(0.2%)	1	(0.2%)	5	(1.0%)
	ENTEROCOLITIS	0	.	1	(0.2%)	0	.	0	.	1	(0.2%)
	ERUCTATION	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	ESOPHAGITIS	0	.	3	(0.6%)	2	(0.4%)	0	.	5	(1.0%)
	FLATULENCE	0	.	4	(0.8%)	4	(0.8%)	0	.	8	(1.7%)
	GASTRIC ULCER	0	.	1	(0.2%)	1	(0.2%)	0	.	2	(0.4%)
	GASTRITIS	0	.	9	(1.9%)	3	(0.6%)	0	.	12	(2.5%)
	GASTROENTERITIS	0	.	9	(1.9%)	3	(0.6%)	1	(0.2%)	13	(2.7%)
	GASTROESOPHAGEAL REFLUX	0	.	2	(0.4%)	0	.	0	.	2	(0.4%)
	GASTROINTESTINAL DISORDER NOS	0	.	4	(0.8%)	3	(0.6%)	0	.	7	(1.5%)
	GI HEMORRHAGE	0	.	0	.	0	.	1	(0.2%)	1	(0.2%)
	GINGIVITIS	0	.	1	(0.2%)	1	(0.2%)	0	.	2	(0.4%)
	HEMATEMESIS	0	.	1	(0.2%)	1	(0.2%)	0	.	2	(0.4%)
	HEMORRHAGE RECTUM	0	.	2	(0.4%)	0	.	0	.	2	(0.4%)

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TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499 (N= 480)

WHO BODY SYSTEM	WHO PREFERRED TERM	Missing		Mild		Intensity Moderate		Severe		Total	
GASTROINTESTINAL SYSTEM	HEMORRHOIDS	0	.	5	(1.0%)	1	(0.2%)	2	(0.4%)	8	(1.7%)
	ILEUS	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	INTESTINAL OBSTRUCTION	0	.	1	(0.2%)	0	.	3	(0.6%)	4	(0.8%)
	IRRITABLE BOWEL SYNDROME	0	.	1	(0.2%)	0	.	0	.	1	(0.2%)
	LACTOSE INTOLERANCE	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	MEGACOLON ACQUIRED	0	.	1	(0.2%)	0	.	0	.	1	(0.2%)
	MELENA	0	.	6	(1.3%)	0	.	0	.	6	(1.3%)
	NAUSEA	0	.	23	(4.8%)	13	(2.7%)	2	(0.4%)	38	(7.9%)
	PANCREATITIS	0	.	0	.	0	.	1	(0.2%)	1	(0.2%)
	PERIODONTITIS	0	.	5	(1.0%)	6	(1.3%)	1	(0.2%)	12	(2.5%)
	PERITONITIS	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	STOMATITIS	0	.	2	(0.4%)	1	(0.2%)	0	.	3	(0.6%)
	TENESMUS	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	TONGUE EDEMA	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	TOOTH ACHE	0	.	3	(0.6%)	3	(0.6%)	0	.	6	(1.3%)
	TOOTH DISORDER	0	.	1	(0.2%)	0	.	0	.	1	(0.2%)
	VOMITING	0	.	10	(2.1%)	10	(2.1%)	0	.	20	(4.2%)
HEARING AND VESTIBULAR	TOTAL	0	.	4	(0.8%)	5	(1.0%)	0	.	9	(1.9%)
	DEAFNESS	0	.	1	(0.2%)	1	(0.2%)	0	.	2	(0.4%)
	EAR DISORDER NOS	0	.	2	(0.4%)	1	(0.2%)	0	.	3	(0.6%)
	EARACHE	0	.	2	(0.4%)	1	(0.2%)	0	.	3	(0.6%)
	HEARING DECREASED	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	TINNITUS	0	.	1	(0.2%)	0	.	0	.	1	(0.2%)
	VESTIBULAR DISORDER	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
HEART RATE AND RHYTHM	TOTAL	0	.	30	(6.3%)	16	(3.3%)	2	(0.4%)	48	(10.0%)
	ARRHYTHMIA	0	.	3	(0.6%)	0	.	0	.	3	(0.6%)
	ARRHYTHMIA ATRIAL	0	.	0	.	3	(0.6%)	0	.	3	(0.6%)
	ATRIOVENTRICULAR BLOCK	0	.	2	(0.4%)	0	.	0	.	2	(0.4%)
	BRADYCARDIA	0	.	4	(0.8%)	0	.	1	(0.2%)	5	(1.0%)
	BUNDLE BRANCH BLOCK	0	.	3	(0.6%)	0	.	0	.	3	(0.6%)
	CARDIAC ARREST	0	.	0	.	0	.	1	(0.2%)	1	(0.2%)
	EXTRASYSTOLES	0	.	11	(2.3%)	2	(0.4%)	0	.	13	(2.7%)
	EXTRASYSTOLES	0	.	6	(1.3%)	1	(0.2%)	0	.	7	(1.5%)
	SUPRAVENTRICULAR FIBRILLATION ATRIAL	0	.	4	(0.8%)	5	(1.0%)	0	.	9	(1.9%)

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TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499 (N= 480)

WHO BODY SYSTEM	WHO PREFERRED TERM	Missing		Mild		Intensity Moderate		Severe		Total	
HEART RATE AND RHYTHM	PALPITATION	0	.	3	(0.6%)	1	(0.2%)	0	.	4	(0.8%)
	TACHYCARDIA	0	.	6	(1.3%)	5	(1.0%)	0	.	11	(2.3%)
	TACHYCARDIA	0	.	1	(0.2%)	0	.	0	.	1	(0.2%)
	SUPRAVENTRICULAR										
LIVER AND BILIARY SYSTEM	TOTAL	0	.	13	(2.7%)	18	(3.8%)	5	(1.0%)	36	(7.5%)
	BILIRUBINEMIA	0	.	1	(0.2%)	3	(0.6%)	0	.	4	(0.8%)
	CHOLECYSTITIS	0	.	0	.	0	.	2	(0.4%)	2	(0.4%)
	CHOLELITHIASIS	0	.	1	(0.2%)	2	(0.4%)	1	(0.2%)	4	(0.8%)
	GAMMA-GT INCREASED	0	.	3	(0.6%)	5	(1.0%)	1	(0.2%)	9	(1.9%)
	HEPATIC ENZYMES INCREASED	0	.	5	(1.0%)	5	(1.0%)	2	(0.4%)	12	(2.5%)
	HEPATIC FUNCTION ABNORMAL	0	.	3	(0.6%)	4	(0.8%)	0	.	7	(1.5%)
	HEPATITIS	0	.	1	(0.2%)	0	.	0	.	1	(0.2%)
	LIVER FATTY	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	SGOT INCREASED	0	.	4	(0.8%)	1	(0.2%)	0	.	5	(1.0%)
	SGPT INCREASED	0	.	3	(0.6%)	3	(0.6%)	0	.	6	(1.3%)
METABOLIC AND NUTRITIONAL	TOTAL	0	.	40	(8.3%)	26	(5.4%)	3	(0.6%)	69	(14.4%)
	BLOOD UREA NITROGEN INCREASED	0	.	5	(1.0%)	0	.	0	.	5	(1.0%)
	DEHYDRATION	0	.	0	.	2	(0.4%)	0	.	2	(0.4%)
	DIABETES MELLITUS	0	.	4	(0.8%)	2	(0.4%)	0	.	6	(1.3%)
	DIABETES MELLITUS AGGRAVATED	0	.	2	(0.4%)	1	(0.2%)	0	.	3	(0.6%)
	GLUCOSE TOLERANCE ABNORMAL	0	.	1	(0.2%)	0	.	0	.	1	(0.2%)
	GLYCOSURIA	0	.	3	(0.6%)	1	(0.2%)	0	.	4	(0.8%)
	GOUT	0	.	2	(0.4%)	3	(0.6%)	2	(0.4%)	7	(1.5%)
	HYPERCHOLESTEROLEMIA	0	.	2	(0.4%)	1	(0.2%)	0	.	3	(0.6%)
	HYPERGLYCEMIA	0	.	17	(3.5%)	5	(1.0%)	1	(0.2%)	23	(4.8%)
	HYPERKALEMIA	0	.	1	(0.2%)	1	(0.2%)	0	.	2	(0.4%)
	HYPERLIPEMIA	0	.	1	(0.2%)	2	(0.4%)	0	.	3	(0.6%)
	HYPERNATREMIA	0	.	4	(0.8%)	0	.	0	.	4	(0.8%)
	HYPERURICEMIA	0	.	3	(0.6%)	2	(0.4%)	0	.	5	(1.0%)
	HYPOCHLOREMIA	0	.	1	(0.2%)	0	.	0	.	1	(0.2%)
	HYPOGLYCEMIA	0	.	2	(0.4%)	3	(0.6%)	0	.	5	(1.0%)

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TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499 (N= 480)

WHO BODY SYSTEM	WHO PREFERRED TERM	Missing		Mild		Intensity Moderate		Severe		Total	
METABOLIC AND NUTRITIONAL	HYPONATREMIA	0	.	1	(0.2%)	0	.	0	.	1	(0.2%)
	KETOSIS	0	.	1	(0.2%)	0	.	0	.	1	(0.2%)
	NPN INCREASED	0	.	2	(0.4%)	0	.	0	.	2	(0.4%)
	PHOSPHATASE ALKALINE INCREASED	0	.	1	(0.2%)	2	(0.4%)	0	.	3	(0.6%)
	WEIGHT DECREASE	0	.	6	(1.3%)	5	(1.0%)	0	.	11	(2.3%)
	WEIGHT INCREASE	0	.	1	(0.2%)	0	.	0	.	1	(0.2%)
MUSCULOSKELETAL SYSTEM	TOTAL	0	.	49	(10.2%)	51	(10.6%)	7	(1.5%)	107	(22.3%)
	ARTHRALGIA	0	.	17	(3.5%)	13	(2.7%)	0	.	30	(6.3%)
	ARTHRITIS	0	.	9	(1.9%)	3	(0.6%)	0	.	12	(2.5%)
	ARTHRITIS AGGRAVATED	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	ARTHROPATHY	0	.	1	(0.2%)	0	.	1	(0.2%)	2	(0.4%)
	ARTHROSIS	0	.	3	(0.6%)	1	(0.2%)	0	.	4	(0.8%)
	BACK PAIN	0	.	27	(5.6%)	26	(5.4%)	3	(0.6%)	56	(11.7%)
	BONE DEVELOPMENT ABNORMAL	0	.	0	.	1	(0.2%)	1	(0.2%)	2	(0.4%)
	BONE DISORDER	0	.	0	.	1	(0.2%)	1	(0.2%)	2	(0.4%)
	BURSITIS	0	.	1	(0.2%)	1	(0.2%)	0	.	2	(0.4%)
	DUPUYTREN'S CONTRACTURE	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	MYALGIA	0	.	6	(1.3%)	6	(1.3%)	1	(0.2%)	13	(2.7%)
	OSTEOPOROSIS	0	.	3	(0.6%)	2	(0.4%)	0	.	5	(1.0%)
	SKELETAL PAIN	0	.	2	(0.4%)	4	(0.8%)	0	.	6	(1.3%)
	TENDINITIS	0	.	0	.	3	(0.6%)	0	.	3	(0.6%)
	TENDON DISORDER	0	.	1	(0.2%)	0	.	0	.	1	(0.2%)
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	TOTAL	0	.	5	(1.0%)	11	(2.3%)	2	(0.4%)	18	(3.8%)
	ANGINA PECTORIS	0	.	5	(1.0%)	5	(1.0%)	1	(0.2%)	11	(2.3%)
	ANGINA PECTORIS AGGRAVATED	0	.	0	.	2	(0.4%)	0	.	2	(0.4%)
	CARDIOMYOPATHY	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	CORONARY ARTERY DISORDER	0	.	0	.	2	(0.4%)	0	.	2	(0.4%)
	MYOCARDIAL INFARCTION	0	.	0	.	1	(0.2%)	1	(0.2%)	2	(0.4%)
	MYOCARDIAL ISCHEMIA	0	.	1	(0.2%)	1	(0.2%)	0	.	2	(0.4%)

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SB 207499

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, PREFERRED TERM AND
PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499 (N= 480)

WHO BODY SYSTEM	WHO PREFERRED TERM	Missing	Mild	Intensity Moderate	Severe	Total
NEOPLASM	TOTAL	1 (0.2%)	9 (1.9%)	8 (1.7%)	9 (1.9%)	27 (5.6%)
	ADENOCARCINOMA NOS	0 .	1 (0.2%)	0 .	0 .	1 (0.2%)
	BASAL CELL CARCINOMA	0 .	0 .	1 (0.2%)	0 .	1 (0.2%)
	BREAST FIBROADENOSIS	0 .	0 .	1 (0.2%)	0 .	1 (0.2%)
	BREAST NEOPLASM FEMALE	0 .	2 (0.4%)	0 .	0 .	2 (0.4%)
	CARCINOMA	0 .	0 .	1 (0.2%)	1 (0.2%)	2 (0.4%)
	GI NEOPLASM MALIGNANT	0 .	0 .	0 .	1 (0.2%)	1 (0.2%)
	HEMANGIOMA ACQUIRED	0 .	1 (0.2%)	0 .	0 .	1 (0.2%)
	HEPATIC NEOPLASM	0 .	1 (0.2%)	0 .	0 .	1 (0.2%)
	LIPOMA	0 .	0 .	1 (0.2%)	0 .	1 (0.2%)
	NEOPLASM NOS	0 .	4 (0.8%)	4 (0.8%)	1 (0.2%)	9 (1.9%)
	PULMONARY CARCINOMA	1 (0.2%)	0 .	0 .	6 (1.3%)	7 (1.5%)
PLATELET BLEEDING AND CLOTTING	TOTAL	0 .	2 (0.4%)	3 (0.6%)	0 .	5 (1.0%)
	HEMATOMA	0 .	0 .	1 (0.2%)	0 .	1 (0.2%)
	PURPURA	0 .	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
	THROMBOCYTOPENIA	0 .	1 (0.2%)	1 (0.2%)	0 .	2 (0.4%)
PSYCHIATRIC	TOTAL	0 .	24 (5.0%)	30 (6.3%)	3 (0.6%)	57 (11.9%)
	AGITATION	0 .	0 .	2 (0.4%)	0 .	2 (0.4%)
	AMNESIA	0 .	1 (0.2%)	0 .	0 .	1 (0.2%)
	ANXIETY	0 .	7 (1.5%)	5 (1.0%)	0 .	12 (2.5%)
	CONFUSION	0 .	0 .	2 (0.4%)	1 (0.2%)	3 (0.6%)
	DEPRESSION	0 .	7 (1.5%)	14 (2.9%)	0 .	21 (4.4%)
	DEPRESSION AGGRAVATED	0 .	0 .	1 (0.2%)	0 .	1 (0.2%)
	INSOMNIA	0 .	15 (3.1%)	7 (1.5%)	1 (0.2%)	23 (4.8%)
	NERVOUSNESS	0 .	2 (0.4%)	0 .	0 .	2 (0.4%)
	SOMNOLENCE	0 .	2 (0.4%)	1 (0.2%)	0 .	3 (0.6%)
	SUICIDE ATTEMPT	0 .	0 .	0 .	1 (0.2%)	1 (0.2%)
RED BLOOD CELL	TOTAL	0 .	14 (2.9%)	2 (0.4%)	0 .	16 (3.3%)
	ANEMIA	0 .	6 (1.3%)	2 (0.4%)	0 .	8 (1.7%)
	ANEMIA HYPOCHROMIC	0 .	1 (0.2%)	0 .	0 .	1 (0.2%)
	ERYTHROCYTES ABNORMAL	0 .	1 (0.2%)	0 .	0 .	1 (0.2%)
	POLYCYTHEMIA	0 .	6 (1.3%)	0 .	0 .	6 (1.3%)
REPRODUCTIVE FEMALE	TOTAL	1 (0.2%)	4 (0.8%)	0 .	0 .	5 (1.0%)
	MENSTRUAL DISORDER	0 .	1 (0.2%)	0 .	0 .	1 (0.2%)
	VAGINAL HEMORRHAGE	0 .	1 (0.2%)	0 .	0 .	1 (0.2%)
	VAGINITIS	1 (0.2%)	2 (0.4%)	0 .	0 .	3 (0.6%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM, PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE EVENT FOR EACH PATIENT

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499 (N= 480)

WHO BODY SYSTEM	WHO PREFERRED TERM	Missing		Mild		Intensity Moderate		Severe		Total	
REPRODUCTIVE MALE	TOTAL	0	.	6	(1.3%)	4	(0.8%)	3	(0.6%)	13	(2.7%)
	IMPOTENCE	0	.	2	(0.4%)	2	(0.4%)	2	(0.4%)	6	(1.3%)
	PROSTATIC DISORDER	0	.	3	(0.6%)	2	(0.4%)	1	(0.2%)	6	(1.3%)
	TESTIS DISORDER	0	.	1	(0.2%)	0	.	0	.	1	(0.2%)
RESISTANCE MECHANISM	TOTAL	0	.	65	(13.5%)	37	(7.7%)	9	(1.9%)	111	(23.1%)
	ABSCESS	0	.	1	(0.2%)	3	(0.6%)	0	.	4	(0.8%)
	HERPES SIMPLEX	0	.	2	(0.4%)	1	(0.2%)	0	.	3	(0.6%)
	HERPES ZOSTER	0	.	1	(0.2%)	4	(0.8%)	3	(0.6%)	8	(1.7%)
	INFECTION	0	.	5	(1.0%)	5	(1.0%)	1	(0.2%)	11	(2.3%)
	INFECTION BACTERIAL	0	.	2	(0.4%)	0	.	0	.	2	(0.4%)
	INFECTION FUNGAL	0	.	2	(0.4%)	0	.	0	.	2	(0.4%)
	INFECTION VIRAL	0	.	22	(4.6%)	14	(2.9%)	3	(0.6%)	39	(8.1%)
	MONILIASIS	0	.	6	(1.3%)	0	.	0	.	6	(1.3%)
	MONILIASIS GENITAL	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	OTITIS MEDIA	0	.	2	(0.4%)	3	(0.6%)	0	.	5	(1.0%)
	SEPSIS	0	.	0	.	1	(0.2%)	1	(0.2%)	2	(0.4%)
	UPPER RESP TRACT INFECTION	0	.	36	(7.5%)	14	(2.9%)	1	(0.2%)	51	(10.6%)
RESPIRATORY SYSTEM	TOTAL	0	.	80	(16.7%)	226	(47.1%)	51	(10.6%)	357	(74.4%)
	APNEA	0	.	1	(0.2%)	0	.	0	.	1	(0.2%)
	ASTHMA	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	BRONCHITIS	0	.	5	(1.0%)	7	(1.5%)	2	(0.4%)	14	(2.9%)
	CHEST X-RAY ABNORMAL	0	.	3	(0.6%)	0	.	0	.	3	(0.6%)
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	0	.	66	(13.8%)	224	(46.7%)	37	(7.7%)	327	(68.1%)
	COUGHING	0	.	21	(4.4%)	9	(1.9%)	1	(0.2%)	31	(6.5%)
	DYSPNEA	0	.	5	(1.0%)	8	(1.7%)	0	.	13	(2.7%)
	EPISTAXIS	0	.	2	(0.4%)	0	.	1	(0.2%)	3	(0.6%)
	HEMOPTYSIS	0	.	6	(1.3%)	1	(0.2%)	0	.	7	(1.5%)
	HYPOXIA	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	LARYNGITIS	0	.	1	(0.2%)	1	(0.2%)	0	.	2	(0.4%)
	PHARYNGITIS	0	.	32	(6.7%)	10	(2.1%)	0	.	42	(8.8%)
	PLEURAL EFFUSION	0	.	0	.	0	.	1	(0.2%)	1	(0.2%)
	PLEURAL PAIN	0	.	1	(0.2%)	0	.	1	(0.2%)	2	(0.4%)
	PLEURISY	0	.	1	(0.2%)	0	.	1	(0.2%)	2	(0.4%)
	PNEUMONIA	0	.	1	(0.2%)	5	(1.0%)	8	(1.7%)	14	(2.9%)
	PNEUMONIA LOBAR	0	.	0	.	0	.	1	(0.2%)	1	(0.2%)
	RESPIRATORY DISORDER	0	.	16	(3.3%)	9	(1.9%)	3	(0.6%)	28	(5.8%)

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TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499 (N= 480)

WHO BODY SYSTEM	WHO PREFERRED TERM	Missing		Mild		Intensity Moderate		Severe		Total	
RESPIRATORY SYSTEM	RESPIRATORY INSUFFICIENCY	0	.	0	.	1	(0.2%)	2	(0.4%)	3	(0.6%)
	RHINITIS	0	.	39	(8.1%)	4	(0.8%)	1	(0.2%)	44	(9.2%)
	SINUSITIS	0	.	6	(1.3%)	10	(2.1%)	0	.	16	(3.3%)
	SPUTUM INCREASED	0	.	6	(1.3%)	0	.	0	.	6	(1.3%)
	TRACHEITIS	0	.	1	(0.2%)	2	(0.4%)	0	.	3	(0.6%)
SKIN AND APPENDAGES	TOTAL	0	.	24	(5.0%)	21	(4.4%)	2	(0.4%)	47	(9.8%)
	ALOPECIA	0	.	0	.	2	(0.4%)	0	.	2	(0.4%)
	ANGIOEDEMA	0	.	1	(0.2%)	0	.	0	.	1	(0.2%)
	BULLOUS ERUPTION	0	.	1	(0.2%)	0	.	0	.	1	(0.2%)
	DERMATITIS	0	.	4	(0.8%)	1	(0.2%)	1	(0.2%)	6	(1.3%)
	DERMATITIS FUNGAL	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	DERMATITIS LICHENOID	0	.	1	(0.2%)	1	(0.2%)	0	.	2	(0.4%)
	ECZEMA	0	.	4	(0.8%)	1	(0.2%)	0	.	5	(1.0%)
	FOLLICULITIS	0	.	2	(0.4%)	0	.	0	.	2	(0.4%)
	HYPERKERATOSIS	0	.	1	(0.2%)	0	.	0	.	1	(0.2%)
	MELANOSIS	0	.	1	(0.2%)	0	.	0	.	1	(0.2%)
	PRURITUS	0	.	9	(1.9%)	4	(0.8%)	1	(0.2%)	14	(2.9%)
	PSORIASIS	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	RASH	0	.	2	(0.4%)	3	(0.6%)	0	.	5	(1.0%)
	RASH ERYTHEMATOUS	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	RASH MACULO-PAPULAR	0	.	2	(0.4%)	1	(0.2%)	0	.	3	(0.6%)
	RASH PUSTULAR	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	SKIN DISORDER	0	.	3	(0.6%)	2	(0.4%)	0	.	5	(1.0%)
	SKIN DRY	0	.	0	.	2	(0.4%)	0	.	2	(0.4%)
	SKIN HYPERTROPHY	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	SKIN ULCERATION	0	.	3	(0.6%)	1	(0.2%)	0	.	4	(0.8%)
	URTICARIA	0	.	3	(0.6%)	4	(0.8%)	0	.	7	(1.5%)
SPECIAL SENSES OTHER	TOTAL	0	.	2	(0.4%)	0	.	0	.	2	(0.4%)
	TASTE PERVERSION	0	.	2	(0.4%)	0	.	0	.	2	(0.4%)
URINARY SYSTEM	TOTAL	0	.	44	(9.2%)	12	(2.5%)	9	(1.9%)	65	(13.5%)
	ALBUMINURIA	0	.	11	(2.3%)	1	(0.2%)	0	.	12	(2.5%)
	BLADDER CALCULUS	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	CYSTITIS	0	.	4	(0.8%)	1	(0.2%)	0	.	5	(1.0%)
	DYSURIA	0	.	2	(0.4%)	1	(0.2%)	0	.	3	(0.6%)
	HEMATURIA	0	.	11	(2.3%)	2	(0.4%)	0	.	13	(2.7%)
	MICTURITION DISORDER	0	.	1	(0.2%)	0	.	0	.	1	(0.2%)

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TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499 (N= 480)

WHO BODY SYSTEM	WHO PREFERRED TERM	Intensity					Total		
		Missing	Mild	Moderate	Severe				
URINARY SYSTEM	MICTURITION FREQUENCY	0	.	3 (0.6%)	0	.	0	.	3 (0.6%)
	NOCTURIA	0	.	1 (0.2%)	0	.	0	.	1 (0.2%)
	PYELONEPHRITIS	0	.	0	0	.	2 (0.4%)	.	2 (0.4%)
	PYURIA	0	.	11 (2.3%)	1 (0.2%)	0	.	12 (2.5%)	
	RENAL CALCULUS	0	.	1 (0.2%)	0	.	0	.	1 (0.2%)
	RENAL CYST	0	.	1 (0.2%)	0	.	0	.	1 (0.2%)
	RENAL FAILURE ACUTE	0	.	0	0	.	2 (0.4%)	.	2 (0.4%)
	RENAL FUNCTION ABNORMAL	0	.	1 (0.2%)	0	.	0	.	1 (0.2%)
	RENAL PAIN	0	.	2 (0.4%)	0	.	1 (0.2%)	.	3 (0.6%)
	URINARY INCONTINENCE	0	.	1 (0.2%)	1 (0.2%)	0	.	2 (0.4%)	
	URINARY RETENTION	0	.	1 (0.2%)	0	.	3 (0.6%)	.	4 (0.8%)
	URINARY TRACT INFECTION	0	.	12 (2.5%)	9 (1.9%)	1 (0.2%)	22 (4.6%)		
	URINE ABNORMAL	0	.	1 (0.2%)	0	.	0	.	1 (0.2%)
	VASCULAR EXTRACARDIAC	TOTAL	0	.	8 (1.7%)	10 (2.1%)	2 (0.4%)	20 (4.2%)	
ARTERIOSCLEROSIS		0	.	1 (0.2%)	0	.	0	.	1 (0.2%)
CEREBROVASCULAR DISORDER		0	.	1 (0.2%)	3 (0.6%)	0	.	4 (0.8%)	
CLAUDICATION INTERMITTENT		0	.	1 (0.2%)	0	.	0	.	1 (0.2%)
CRAMPS LEGS		0	.	0	2 (0.4%)	0	.	2 (0.4%)	
PERIPHERAL ISCHEMIA		0	.	0	1 (0.2%)	0	.	1 (0.2%)	
PHLEBITIS		0	.	0	1 (0.2%)	0	.	1 (0.2%)	
PHLEBITIS SUPERFICIAL		0	.	1 (0.2%)	0	.	0	.	1 (0.2%)
THROMBOPHLEBITIS LEG		0	.	1 (0.2%)	0	.	0	.	1 (0.2%)
THROMBOPHLEBITIS RETINAL VEIN		0	.	1 (0.2%)	0	.	0	.	1 (0.2%)
THROMBOSIS ARTERIAL LEG		0	.	0	1 (0.2%)	0	.	1 (0.2%)	
THROMBOSIS RETINAL ARTERY		0	.	0	2 (0.4%)	0	.	2 (0.4%)	
VASCULAR DISORDER		0	.	1 (0.2%)	0	.	2 (0.4%)	.	3 (0.6%)
VEIN DISORDER		0	.	1 (0.2%)	0	.	0	.	1 (0.2%)
VEIN VARICOSE	0	.	2 (0.4%)	1 (0.2%)	0	.	3 (0.6%)		
VISION	TOTAL	0	.	12 (2.5%)	7 (1.5%)	2 (0.4%)	21 (4.4%)		
	BLEPHARITIS	0	.	1 (0.2%)	0	.	0	.	1 (0.2%)
	CATARACT	0	.	2 (0.4%)	3 (0.6%)	1 (0.2%)	6 (1.3%)		

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INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499 (N= 480)

WHO BODY SYSTEM	WHO PREFERRED TERM	Missing		Mild		Intensity Moderate		Severe		Total	
VISION	CONJUNCTIVAL HEMORRHAGE	0	.	0	.	0	.	1	(0.2%)	1	(0.2%)
	CONJUNCTIVITIS	0	.	8	(1.7%)	0	.	0	.	8	(1.7%)
	CORNEAL ULCERATION	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	EYE ABNORMALITY	0	.	1	(0.2%)	1	(0.2%)	0	.	2	(0.4%)
	GLAUCOMA	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	UVEITIS	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	VISION ABNORMAL	0	.	0	.	1	(0.2%)	0	.	1	(0.2%)
	VISUAL FIELD DEFECT	0	.	1	(0.2%)	0	.	0	.	1	(0.2%)
WHITE CELL AND RETICULOENDOTHELIAL SYSTE	TOTAL	0	.	18	(3.8%)	5	(1.0%)	0	.	23	(4.8%)
	EOSINOPHILIA	0	.	2	(0.4%)	0	.	0	.	2	(0.4%)
	GRANULOCYTOPENIA	0	.	2	(0.4%)	0	.	0	.	2	(0.4%)
	LEUKOCYTOSIS	0	.	13	(2.7%)	4	(0.8%)	0	.	17	(3.5%)
	LEUKOPENIA	0	.	2	(0.4%)	0	.	0	.	2	(0.4%)
	LYMPHADENOPATHY	0	.	1	(0.2%)	1	(0.2%)	0	.	2	(0.4%)
	LYMPHADENOPATHY	0	.	1	(0.2%)	0	.	0	.	1	(0.2%)
	CERVICAL LYMPHOPENIA	0	.	1	(0.2%)	0	.	0	.	1	(0.2%)

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TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL (N= 723)

WHO BODY SYSTEM	WHO PREFERRED TERM	Missing		Mild		Intensity Moderate		Severe		Total	
TOTAL	TOTAL	0	.	108	(14.9%)	390	(53.9%)	177	(24.5%)	675	(93.4%)
APPLICATION SITE	TOTAL	0	.	4	(0.6%)	3	(0.4%)	1	(0.1%)	8	(1.1%)
	INJECTION SITE	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	INFLAMMATION										
	OTITIS EXTERNA	0	.	4	(0.6%)	3	(0.4%)	1	(0.1%)	8	(1.1%)
	TYMPANIC MEMBRANE PERFORATION	0	.	1	(0.1%)	0	.	0	.	1	(0.1%)
AUTONOMIC NERVOUS SYSTEM	TOTAL	0	.	3	(0.4%)	3	(0.4%)	1	(0.1%)	7	(1.0%)
	MOUTH DRY	0	.	2	(0.3%)	1	(0.1%)	0	.	3	(0.4%)
	SWEATING INCREASED	0	.	1	(0.1%)	2	(0.3%)	1	(0.1%)	4	(0.6%)
BODY AS A WHOLE GENERAL	TOTAL	0	.	81	(11.2%)	105	(14.5%)	18	(2.5%)	204	(28.2%)
	ALCOHOL INTOLERANCE	0	.	0	.	0	.	1	(0.1%)	1	(0.1%)
	ALLERGIC REACTION	0	.	2	(0.3%)	2	(0.3%)	0	.	4	(0.6%)
	ASTHENIA	0	.	12	(1.7%)	9	(1.2%)	2	(0.3%)	23	(3.2%)
	CELLULITIS	0	.	2	(0.3%)	2	(0.3%)	1	(0.1%)	5	(0.7%)
	CHEST PAIN	0	.	18	(2.5%)	19	(2.6%)	4	(0.6%)	41	(5.7%)
	CHEST PAIN PRECORDIAL	0	.	5	(0.7%)	1	(0.1%)	0	.	6	(0.8%)
	CHEST PAIN SUBSTERNAL	0	.	2	(0.3%)	0	.	0	.	2	(0.3%)
	DRUG LEVEL INCREASED	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	EDEMA	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	EDEMA DEPENDENT	0	.	7	(1.0%)	0	.	0	.	7	(1.0%)
	EDEMA LEGS	0	.	9	(1.2%)	1	(0.1%)	0	.	10	(1.4%)
	FACE EDEMA	0	.	1	(0.1%)	0	.	0	.	1	(0.1%)
	FATIGUE	0	.	8	(1.1%)	9	(1.2%)	0	.	17	(2.4%)
	FEVER	0	.	16	(2.2%)	2	(0.3%)	1	(0.1%)	19	(2.6%)
	HOT FLUSHES	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	INFLUENZA-LIKE SYMPTOMS	0	.	0	.	4	(0.6%)	0	.	4	(0.6%)
	INJURY	0	.	28	(3.9%)	49	(6.8%)	11	(1.5%)	88	(12.2%)
	MALAISE	0	.	12	(1.7%)	4	(0.6%)	0	.	16	(2.2%)
	PAIN	0	.	15	(2.1%)	16	(2.2%)	0	.	31	(4.3%)
	RIGORS	0	.	1	(0.1%)	1	(0.1%)	0	.	2	(0.3%)
	THERAPEUTIC RESPONSE INCREASED	0	.	1	(0.1%)	2	(0.3%)	0	.	3	(0.4%)

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TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL (N= 723)

WHO BODY SYSTEM	WHO PREFERRED TERM	Missing	Mild	Intensity Moderate	Severe	Total
CARDIOVASCULAR GENERAL	TOTAL	0	35 (4.8%)	39 (5.4%)	7 (1.0%)	81 (11.2%)
	ANEURYSM	0	0	1 (0.1%)	2 (0.3%)	3 (0.4%)
	CARDIAC FAILURE	0	1 (0.1%)	3 (0.4%)	1 (0.1%)	5 (0.7%)
	CARDIOMEGALY	0	2 (0.3%)	1 (0.1%)	0	3 (0.4%)
	COR PULMONALE	0	0	1 (0.1%)	0	1 (0.1%)
	CYANOSIS	0	0	1 (0.1%)	0	1 (0.1%)
	ECG ABNORMAL	0	3 (0.4%)	0	0	3 (0.4%)
	ECG ABNORMAL SPECIFIC	0	1 (0.1%)	2 (0.3%)	0	3 (0.4%)
	HEART VALVE DISORDERS	0	0	1 (0.1%)	0	1 (0.1%)
	HYPERTENSION	0	26 (3.6%)	15 (2.1%)	1 (0.1%)	42 (5.8%)
	HYPERTENSION AGGRAVATED	0	1 (0.1%)	6 (0.8%)	1 (0.1%)	8 (1.1%)
	HYPERTENSION PULMONARY	0	0	0	1 (0.1%)	1 (0.1%)
	HYPOTENSION	0	4 (0.6%)	2 (0.3%)	0	6 (0.8%)
	HYPOTENSION POSTURAL	0	4 (0.6%)	1 (0.1%)	0	5 (0.7%)
	SYNCOPE	0	4 (0.6%)	7 (1.0%)	1 (0.1%)	12 (1.7%)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	TOTAL	0	78 (10.8%)	67 (9.3%)	8 (1.1%)	153 (21.2%)
	ATAXIA	0	0	1 (0.1%)	0	1 (0.1%)
	COMA	0	0	1 (0.1%)	0	1 (0.1%)
	CONVULSIONS	0	0	1 (0.1%)	1 (0.1%)	2 (0.3%)
	DIZZINESS	0	17 (2.4%)	16 (2.2%)	1 (0.1%)	34 (4.7%)
	DYSPHONIA	0	5 (0.7%)	0	0	5 (0.7%)
	EXTRAPYRAMIDAL DISORDER	0	2 (0.3%)	0	0	2 (0.3%)
	HEADACHE	0	47 (6.5%)	30 (4.1%)	2 (0.3%)	79 (10.9%)
	HYPERTONIA	0	2 (0.3%)	2 (0.3%)	0	4 (0.6%)
	HYPESTHESIA	0	0	1 (0.1%)	0	1 (0.1%)
	MIGRAINE	0	1 (0.1%)	3 (0.4%)	0	4 (0.6%)
	MUSCLE CONTRACTIONS INVOLUNTARY	0	2 (0.3%)	1 (0.1%)	0	3 (0.4%)
	NERVE ROOT LESION	0	1 (0.1%)	0	0	1 (0.1%)
	NEURALGIA	0	4 (0.6%)	12 (1.7%)	2 (0.3%)	18 (2.5%)
	NEUROPATHY	0	0	1 (0.1%)	0	1 (0.1%)
	NEUROPATHY PERIPHERAL	0	0	2 (0.3%)	0	2 (0.3%)
	PARESIS	0	2 (0.3%)	1 (0.1%)	0	3 (0.4%)
	PARESTHESIA	0	3 (0.4%)	1 (0.1%)	0	4 (0.6%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM, PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE EVENT FOR EACH PATIENT

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL (N= 723)

WHO BODY SYSTEM	WHO PREFERRED TERM	Missing		Mild		Intensity Moderate		Severe		Total	
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	PARKINSONISM AGGRAVATED	0	.	0	.	0	.	1	(0.1%)	1	(0.1%)
	TREMOR	0	.	4	(0.6%)	2	(0.3%)	0	.	6	(0.8%)
	TRIGEMINAL NEURALGIA	0	.	0	.	0	.	1	(0.1%)	1	(0.1%)
	VERTIGO	0	.	9	(1.2%)	8	(1.1%)	1	(0.1%)	18	(2.5%)
	WITHDRAWAL HEADACHE	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
COLLAGEN	TOTAL	0	.	0	.	3	(0.4%)	0	.	3	(0.4%)
	ARTHRITIS RHEUMATOID	0	.	0	.	2	(0.3%)	0	.	2	(0.3%)
	ARTHRITIS RHEUMATOID AGGRAVATED	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
ENDOCRINE	TOTAL	0	.	8	(1.1%)	4	(0.6%)	1	(0.1%)	13	(1.8%)
	GOITRE	0	.	1	(0.1%)	1	(0.1%)	0	.	2	(0.3%)
	HYPERTHYROIDISM	0	.	5	(0.7%)	1	(0.1%)	1	(0.1%)	7	(1.0%)
	HYPOTHYROIDISM	0	.	2	(0.3%)	1	(0.1%)	0	.	3	(0.4%)
	MASTITIS MALE	0	.	1	(0.1%)	0	.	0	.	1	(0.1%)
	SIALOADENITIS	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	THYROIDITIS	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
FETAL	TOTAL	0	.	1	(0.1%)	0	.	0	.	1	(0.1%)
	SPINE MALFORMATION	0	.	1	(0.1%)	0	.	0	.	1	(0.1%)
GASTROINTESTINAL SYSTEM	TOTAL	0	.	177	(24.5%)	127	(17.6%)	26	(3.6%)	330	(45.6%)
	ABDOMINAL PAIN	0	.	63	(8.7%)	42	(5.8%)	8	(1.1%)	113	(15.6%)
	ANOREXIA	0	.	5	(0.7%)	5	(0.7%)	0	.	10	(1.4%)
	ANUS DISORDER	0	.	2	(0.3%)	1	(0.1%)	0	.	3	(0.4%)
	APPETITE INCREASED	0	.	1	(0.1%)	0	.	0	.	1	(0.1%)
	COLITIS	0	.	2	(0.3%)	0	.	0	.	2	(0.3%)
	CONSTIPATION	0	.	13	(1.8%)	7	(1.0%)	0	.	20	(2.8%)
	DIARRHEA	0	.	57	(7.9%)	36	(5.0%)	2	(0.3%)	95	(13.1%)
	DIARRHEA BLOODY	0	.	1	(0.1%)	0	.	0	.	1	(0.1%)
	DIVERTICULITIS	0	.	2	(0.3%)	0	.	0	.	2	(0.3%)
	DUODENAL ULCER	0	.	0	.	0	.	1	(0.1%)	1	(0.1%)
	DUODENITIS	0	.	2	(0.3%)	0	.	1	(0.1%)	3	(0.4%)
	DYSPEPSIA	0	.	44	(6.1%)	18	(2.5%)	3	(0.4%)	65	(9.0%)
	DYSPHAGIA	0	.	3	(0.4%)	1	(0.1%)	1	(0.1%)	5	(0.7%)
	ENTERITIS	0	.	2	(0.3%)	0	.	0	.	2	(0.3%)
	ENTEROCOLITIS	0	.	1	(0.1%)	0	.	0	.	1	(0.1%)

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TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL (N= 723)

WHO BODY SYSTEM	WHO PREFERRED TERM	Missing		Mild		Intensity Moderate		Severe		Total	
GASTROINTESTINAL SYSTEM	ERUCTATION	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	ESOPHAGITIS	0	.	4	(0.6%)	4	(0.6%)	0	.	8	(1.1%)
	ESOPHAGOSPASM	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	FLATULENCE	0	.	8	(1.1%)	5	(0.7%)	0	.	13	(1.8%)
	GASTRIC ULCER	0	.	1	(0.1%)	1	(0.1%)	0	.	2	(0.3%)
	GASTRITIS	0	.	12	(1.7%)	6	(0.8%)	0	.	18	(2.5%)
	GASTROENTERITIS	0	.	12	(1.7%)	11	(1.5%)	1	(0.1%)	24	(3.3%)
	GASTROESOPHAGEAL REFLUX	0	.	4	(0.6%)	1	(0.1%)	0	.	5	(0.7%)
	GASTROINTESTINAL DISORDER NOS	0	.	7	(1.0%)	5	(0.7%)	0	.	12	(1.7%)
	GI HEMORRHAGE	0	.	0	.	2	(0.3%)	2	(0.3%)	4	(0.6%)
	GINGIVITIS	0	.	1	(0.1%)	1	(0.1%)	0	.	2	(0.3%)
	HEMATEMESIS	0	.	1	(0.1%)	1	(0.1%)	0	.	2	(0.3%)
	HEMORRHAGE RECTUM	0	.	3	(0.4%)	0	.	0	.	3	(0.4%)
	HEMORRHOIDS	0	.	7	(1.0%)	1	(0.1%)	2	(0.3%)	10	(1.4%)
	ILEUS	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	INTESTINAL OBSTRUCTION	0	.	1	(0.1%)	1	(0.1%)	3	(0.4%)	5	(0.7%)
	IRRITABLE BOWEL SYNDROME	1	(0.1%)	1	(0.1%)	0	.	0	.	2	(0.3%)
	LACTOSE INTOLERANCE	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	MEGACOLON ACQUIRED	0	.	1	(0.1%)	0	.	0	.	1	(0.1%)
	MELENA	0	.	8	(1.1%)	3	(0.4%)	0	.	11	(1.5%)
	NAUSEA	0	.	47	(6.5%)	23	(3.2%)	2	(0.3%)	72	(10.0%)
	PANCREATITIS	0	.	1	(0.1%)	0	.	1	(0.1%)	2	(0.3%)
	PERIODONTITIS	0	.	7	(1.0%)	8	(1.1%)	2	(0.3%)	17	(2.4%)
	PERITONITIS	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	PROCTITIS	0	.	1	(0.1%)	0	.	0	.	1	(0.1%)
	STOMATITIS	0	.	2	(0.3%)	2	(0.3%)	0	.	4	(0.6%)
	TENESMUS	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	TONGUE EDEMA	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	TOOTH ACHE	0	.	5	(0.7%)	3	(0.4%)	0	.	8	(1.1%)
	TOOTH CARIES	0	.	2	(0.3%)	0	.	0	.	2	(0.3%)
	TOOTH DISORDER	0	.	2	(0.3%)	0	.	0	.	2	(0.3%)
	VOMITING	0	.	18	(2.5%)	16	(2.2%)	1	(0.1%)	35	(4.8%)
HEARING AND VESTIBULAR	TOTAL	0	.	9	(1.2%)	8	(1.1%)	0	.	17	(2.4%)
	DEAFNESS	0	.	2	(0.3%)	1	(0.1%)	0	.	3	(0.4%)
	EAR DISORDER NOS	0	.	3	(0.4%)	3	(0.4%)	0	.	6	(0.8%)

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TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL (N= 723)

WHO BODY SYSTEM	WHO PREFERRED TERM	Missing		Mild		Intensity Moderate		Severe		Total	
HEARING AND VESTIBULAR	EARACHE	0	.	3	(0.4%)	1	(0.1%)	0	.	4	(0.6%)
	HEARING DECREASED	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	TINNITUS	0	.	3	(0.4%)	0	.	0	.	3	(0.4%)
	VESTIBULAR DISORDER	0	.	0	.	2	(0.3%)	0	.	2	(0.3%)
HEART RATE AND RHYTHM	TOTAL	0	.	52	(7.2%)	23	(3.2%)	4	(0.6%)	79	(10.9%)
	ARRHYTHMIA	0	.	5	(0.7%)	1	(0.1%)	1	(0.1%)	7	(1.0%)
	ARRHYTHMIA ATRIAL	0	.	0	.	3	(0.4%)	1	(0.1%)	4	(0.6%)
	ATRIOVENTRICULAR BLOCK	0	.	2	(0.3%)	0	.	0	.	2	(0.3%)
	BRADYCARDIA	0	.	11	(1.5%)	0	.	1	(0.1%)	12	(1.7%)
	BUNDLE BRANCH BLOCK	0	.	5	(0.7%)	0	.	0	.	5	(0.7%)
	CARDIAC ARREST	0	.	0	.	0	.	1	(0.1%)	1	(0.1%)
	EXTRASYSTOLES	0	.	15	(2.1%)	2	(0.3%)	0	.	17	(2.4%)
	EXTRASYSTOLES	0	.	10	(1.4%)	2	(0.3%)	0	.	12	(1.7%)
	SUPRAVENTRICULAR FIBRILLATION ATRIAL	0	.	5	(0.7%)	7	(1.0%)	0	.	12	(1.7%)
	PALPITATION	0	.	3	(0.4%)	1	(0.1%)	0	.	4	(0.6%)
	QT INCREASED	0	.	1	(0.1%)	0	.	0	.	1	(0.1%)
	TACHYCARDIA	0	.	13	(1.8%)	8	(1.1%)	0	.	21	(2.9%)
	TACHYCARDIA	0	.	1	(0.1%)	0	.	0	.	1	(0.1%)
	SUPRAVENTRICULAR										
LIVER AND BILIARY SYSTEM	TOTAL	0	.	21	(2.9%)	22	(3.0%)	6	(0.8%)	49	(6.8%)
	BILIRUBINEMIA	0	.	2	(0.3%)	3	(0.4%)	0	.	5	(0.7%)
	CHOLECYSTITIS	0	.	0	.	0	.	2	(0.3%)	2	(0.3%)
	CHOLELITHIASIS	0	.	3	(0.4%)	2	(0.3%)	1	(0.1%)	6	(0.8%)
	GAMMA-GT INCREASED	0	.	7	(1.0%)	7	(1.0%)	2	(0.3%)	16	(2.2%)
	HEPATIC CIRRHOSIS	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	HEPATIC ENZYMES INCREASED	0	.	8	(1.1%)	5	(0.7%)	2	(0.3%)	15	(2.1%)
	HEPATIC FUNCTION ABNORMAL	0	.	3	(0.4%)	4	(0.6%)	0	.	7	(1.0%)
	HEPATITIS	0	.	1	(0.1%)	0	.	0	.	1	(0.1%)
	HEPATITIS INFECTIOUS	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	LIVER FATTY	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	SGOT INCREASED	0	.	4	(0.6%)	1	(0.1%)	0	.	5	(0.7%)
	SGPT INCREASED	0	.	3	(0.4%)	4	(0.6%)	0	.	7	(1.0%)

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TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL (N= 723)

WHO BODY SYSTEM	WHO PREFERRED TERM	Missing		Mild		Intensity Moderate		Severe		Total	
METABOLIC AND NUTRITIONAL	TOTAL	0	.	61	(8.4%)	41	(5.7%)	3	(0.4%)	105	(14.5%)
	BLOOD UREA NITROGEN INCREASED	0	.	5	(0.7%)	0	.	0	.	5	(0.7%)
	DEHYDRATION	0	.	0	.	2	(0.3%)	0	.	2	(0.3%)
	DIABETES MELLITUS	0	.	6	(0.8%)	2	(0.3%)	0	.	8	(1.1%)
	DIABETES MELLITUS AGGRAVATED	0	.	2	(0.3%)	1	(0.1%)	0	.	3	(0.4%)
	GLUCOSE TOLERANCE ABNORMAL	0	.	1	(0.1%)	0	.	0	.	1	(0.1%)
	GLYCOSURIA	0	.	6	(0.8%)	2	(0.3%)	0	.	8	(1.1%)
	GOUT	0	.	3	(0.4%)	7	(1.0%)	2	(0.3%)	12	(1.7%)
	HYPERCHOLESTEROLEMIA	0	.	6	(0.8%)	1	(0.1%)	0	.	7	(1.0%)
	HYPERGLYCEMIA	0	.	23	(3.2%)	7	(1.0%)	1	(0.1%)	31	(4.3%)
	HYPERKALEMIA	0	.	2	(0.3%)	1	(0.1%)	0	.	3	(0.4%)
	HYPERLIPEMIA	0	.	1	(0.1%)	2	(0.3%)	0	.	3	(0.4%)
	HYPERNATREMIA	0	.	4	(0.6%)	1	(0.1%)	0	.	5	(0.7%)
	HYPERTRIGLYCERIDEMIA	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	HYPERURICEMIA	0	.	6	(0.8%)	2	(0.3%)	0	.	8	(1.1%)
	HYPOCHLOREMIA	0	.	2	(0.3%)	0	.	0	.	2	(0.3%)
	HYPOGLYCEMIA	0	.	3	(0.4%)	3	(0.4%)	0	.	6	(0.8%)
	HYPOKALEMIA	0	.	1	(0.1%)	1	(0.1%)	0	.	2	(0.3%)
	HYPONATREMIA	0	.	3	(0.4%)	0	.	0	.	3	(0.4%)
	KETOSIS	0	.	1	(0.1%)	0	.	0	.	1	(0.1%)
	NPN INCREASED	0	.	2	(0.3%)	0	.	0	.	2	(0.3%)
	OBESITY	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	PHOSPHATASE ALKALINE INCREASED	0	.	1	(0.1%)	2	(0.3%)	0	.	3	(0.4%)
	WEIGHT DECREASE	0	.	8	(1.1%)	12	(1.7%)	0	.	20	(2.8%)
	WEIGHT INCREASE	0	.	1	(0.1%)	1	(0.1%)	0	.	2	(0.3%)
MUSCULOSKELETAL SYSTEM	TOTAL	0	.	71	(9.8%)	85	(11.8%)	11	(1.5%)	167	(23.1%)
	ARTHRALGIA	0	.	21	(2.9%)	29	(4.0%)	0	.	50	(6.9%)
	ARTHRITIS	0	.	13	(1.8%)	5	(0.7%)	1	(0.1%)	19	(2.6%)
	ARTHRITIS AGGRAVATED	0	.	1	(0.1%)	2	(0.3%)	0	.	3	(0.4%)
	ARTHROPATHY	0	.	3	(0.4%)	0	.	1	(0.1%)	4	(0.6%)
	ARTHROSIS	0	.	4	(0.6%)	2	(0.3%)	0	.	6	(0.8%)
	BACK PAIN	0	.	36	(5.0%)	40	(5.5%)	3	(0.4%)	79	(10.9%)
	BONE DEVELOPMENT ABNORMAL	0	.	0	.	1	(0.1%)	1	(0.1%)	2	(0.3%)

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TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL (N= 723)

WHO BODY SYSTEM	WHO PREFERRED TERM	Missing		Mild		Intensity Moderate		Severe		Total	
MUSCULOSKELETAL SYSTEM	BONE DISORDER	0	.	0	.	1	(0.1%)	1	(0.1%)	2	(0.3%)
	BURSITIS	0	.	1	(0.1%)	1	(0.1%)	0	.	2	(0.3%)
	DUPUYTREN'S CONTRACTURE	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	MYALGIA	0	.	12	(1.7%)	12	(1.7%)	2	(0.3%)	26	(3.6%)
	MYOSITIS	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	OSTEONECROSIS	0	.	0	.	0	.	1	(0.1%)	1	(0.1%)
	OSTEOPOROSIS	0	.	4	(0.6%)	2	(0.3%)	0	.	6	(0.8%)
	SKELETAL PAIN	0	.	3	(0.4%)	5	(0.7%)	0	.	8	(1.1%)
	TENDINITIS	0	.	0	.	3	(0.4%)	0	.	3	(0.4%)
	TENDON DISORDER	0	.	1	(0.1%)	0	.	1	(0.1%)	2	(0.3%)
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	TOTAL	0	.	7	(1.0%)	15	(2.1%)	5	(0.7%)	27	(3.7%)
	ANGINA PECTORIS	0	.	7	(1.0%)	8	(1.1%)	3	(0.4%)	18	(2.5%)
	ANGINA PECTORIS AGGRAVATED	0	.	0	.	2	(0.3%)	0	.	2	(0.3%)
	AORTIC STENOSIS	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	CARDIOMYOPATHY	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	CORONARY ARTERY DISORDER	0	.	0	.	2	(0.3%)	0	.	2	(0.3%)
	MYOCARDIAL INFARCTION	0	.	0	.	1	(0.1%)	2	(0.3%)	3	(0.4%)
	MYOCARDIAL ISCHEMIA	0	.	1	(0.1%)	1	(0.1%)	0	.	2	(0.3%)
NEOPLASM	TOTAL	1	(0.1%)	14	(1.9%)	15	(2.1%)	20	(2.8%)	50	(6.9%)
	ADENOCARCINOMA NOS	0	.	1	(0.1%)	0	.	1	(0.1%)	2	(0.3%)
	BASAL CELL CARCINOMA	0	.	1	(0.1%)	1	(0.1%)	0	.	2	(0.3%)
	BLADDER CARCINOMA	0	.	0	.	0	.	2	(0.3%)	2	(0.3%)
	BREAST FIBROADENOSIS	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	BREAST NEOPLASM FEMALE	0	.	2	(0.3%)	0	.	0	.	2	(0.3%)
	CARCINOMA	0	.	0	.	3	(0.4%)	2	(0.3%)	5	(0.7%)
	COLON CARCINOMA	0	.	0	.	0	.	1	(0.1%)	1	(0.1%)
	GASTRIC CARCINOMA	0	.	0	.	0	.	1	(0.1%)	1	(0.1%)
	GI NEOPLASM MALIGNANT	0	.	0	.	0	.	1	(0.1%)	1	(0.1%)
	HEMANGIOMA ACQUIRED	0	.	1	(0.1%)	0	.	0	.	1	(0.1%)
	HEPATIC NEOPLASM	0	.	1	(0.1%)	0	.	0	.	1	(0.1%)
	LIPOMA	0	.	2	(0.3%)	1	(0.1%)	0	.	3	(0.4%)
	LYMPHOMA MALIGNANT	0	.	0	.	0	.	1	(0.1%)	1	(0.1%)
	NEOPLASM MALIGNANT	0	.	0	.	0	.	1	(0.1%)	1	(0.1%)

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3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE EVENT FOR EACH PATIENT

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL (N= 723)

WHO BODY SYSTEM	WHO PREFERRED TERM	Intensity					Total
		Missing	Mild	Moderate	Severe		
NEOPLASM	NEOPLASM NOS	0	.	7 (1.0%)	9 (1.2%)	3 (0.4%)	19 (2.6%)
	PULMONARY CARCINOMA	1 (0.1%)	0	.	0	7 (1.0%)	8 (1.1%)
PLATELET BLEEDING AND CLOTTING	TOTAL	0	.	2 (0.3%)	4 (0.6%)	0	6 (0.8%)
	HEMATOMA	0	.	0	1 (0.1%)	0	1 (0.1%)
	PURPURA	0	.	1 (0.1%)	2 (0.3%)	0	3 (0.4%)
	THROMBOCYTOPENIA	0	.	1 (0.1%)	1 (0.1%)	0	2 (0.3%)
PSYCHIATRIC	TOTAL	0	.	40 (5.5%)	49 (6.8%)	3 (0.4%)	92 (12.7%)
	AGITATION	0	.	0	4 (0.6%)	0	4 (0.6%)
	AMNESIA	0	.	1 (0.1%)	0	0	1 (0.1%)
	ANXIETY	0	.	14 (1.9%)	11 (1.5%)	0	25 (3.5%)
	APATHY	0	.	1 (0.1%)	0	0	1 (0.1%)
	CONCENTRATION IMPAIRED	0	.	0	1 (0.1%)	0	1 (0.1%)
	CONFUSION	0	.	0	2 (0.3%)	1 (0.1%)	3 (0.4%)
	DEPRESSION	0	.	10 (1.4%)	21 (2.9%)	0	31 (4.3%)
	DEPRESSION AGGRAVATED	0	.	0	1 (0.1%)	0	1 (0.1%)
	INSOMNIA	0	.	19 (2.6%)	11 (1.5%)	1 (0.1%)	31 (4.3%)
	NERVOUSNESS	0	.	5 (0.7%)	2 (0.3%)	0	7 (1.0%)
	SOMNOLENCE	0	.	3 (0.4%)	4 (0.6%)	0	7 (1.0%)
	SUICIDE ATTEMPT	0	.	0	0	1 (0.1%)	1 (0.1%)
RED BLOOD CELL	TOTAL	0	.	16 (2.2%)	3 (0.4%)	0	19 (2.6%)
	ANEMIA	0	.	7 (1.0%)	3 (0.4%)	0	10 (1.4%)
	ANEMIA HYPOCHROMIC	0	.	1 (0.1%)	0	0	1 (0.1%)
	ANEMIA MACROCYTIC	0	.	1 (0.1%)	0	0	1 (0.1%)
	ERYTHROCYTES ABNORMAL	0	.	1 (0.1%)	0	0	1 (0.1%)
	POLYCYTHEMIA	0	.	6 (0.8%)	0	0	6 (0.8%)
REPRODUCTIVE FEMALE	TOTAL	1 (0.1%)	4 (0.6%)	1 (0.1%)	0	.	6 (0.8%)
	MENSTRUAL DISORDER	0	.	1 (0.1%)	0	.	1 (0.1%)
	PELVIC INFLAMMATION	0	.	0	1 (0.1%)	0	1 (0.1%)
	VAGINAL HEMORRHAGE	0	.	1 (0.1%)	0	.	1 (0.1%)
	VAGINITIS	1 (0.1%)	2 (0.3%)	0	0	.	3 (0.4%)
REPRODUCTIVE MALE	TOTAL	0	.	14 (1.9%)	11 (1.5%)	3 (0.4%)	28 (3.9%)
	BALANOPOSTHITIS	0	.	1 (0.1%)	0	.	1 (0.1%)
	IMPOTENCE	0	.	3 (0.4%)	3 (0.4%)	2 (0.3%)	8 (1.1%)
	ORCHITIS	0	.	0	1 (0.1%)	0	1 (0.1%)
	PENIS DISORDER	0	.	1 (0.1%)	0	.	1 (0.1%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM, PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE EVENT FOR EACH PATIENT

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL (N= 723)

WHO BODY SYSTEM	WHO PREFERRED TERM	Missing		Mild		Intensity Moderate		Severe		Total	
REPRODUCTIVE MALE	PROSTATIC DISORDER	0	.	9	(1.2%)	7	(1.0%)	1	(0.1%)	17	(2.4%)
	TESTIS DISORDER	0	.	1	(0.1%)	0	.	0	.	1	(0.1%)
RESISTANCE MECHANISM	TOTAL	0	.	87	(12.0%)	64	(8.9%)	10	(1.4%)	161	(22.3%)
	ABSCCESS	0	.	2	(0.3%)	4	(0.6%)	0	.	6	(0.8%)
	HERPES SIMPLEX	0	.	2	(0.3%)	2	(0.3%)	0	.	4	(0.6%)
	HERPES ZOSTER	0	.	1	(0.1%)	6	(0.8%)	3	(0.4%)	10	(1.4%)
	INFECTION	0	.	8	(1.1%)	8	(1.1%)	1	(0.1%)	17	(2.4%)
	INFECTION BACTERIAL	0	.	2	(0.3%)	0	.	0	.	2	(0.3%)
	INFECTION FUNGAL	0	.	6	(0.8%)	0	.	0	.	6	(0.8%)
	INFECTION VIRAL	0	.	31	(4.3%)	26	(3.6%)	3	(0.4%)	60	(8.3%)
	MONILIASIS	0	.	8	(1.1%)	1	(0.1%)	0	.	9	(1.2%)
	MONILIASIS GENITAL	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	OTITIS MEDIA	0	.	3	(0.4%)	5	(0.7%)	0	.	8	(1.1%)
	SEPSIS	0	.	0	.	1	(0.1%)	2	(0.3%)	3	(0.4%)
	UPPER RESP TRACT INFECTION	0	.	47	(6.5%)	23	(3.2%)	1	(0.1%)	71	(9.8%)
RESPIRATORY SYSTEM	TOTAL	0	.	121	(16.7%)	331	(45.8%)	79	(10.9%)	531	(73.4%)
	APNEA	0	.	1	(0.1%)	1	(0.1%)	0	.	2	(0.3%)
	ASTHMA	0	.	1	(0.1%)	2	(0.3%)	0	.	3	(0.4%)
	BRONCHITIS	0	.	7	(1.0%)	13	(1.8%)	2	(0.3%)	22	(3.0%)
	CHEST X-RAY ABNORMAL	0	.	3	(0.4%)	0	.	0	.	3	(0.4%)
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	0	.	101	(14.0%)	321	(44.4%)	60	(8.3%)	482	(66.7%)
	COUGHING	0	.	31	(4.3%)	12	(1.7%)	1	(0.1%)	44	(6.1%)
	DYSPNEA	0	.	9	(1.2%)	12	(1.7%)	0	.	21	(2.9%)
	EPISTAXIS	0	.	3	(0.4%)	0	.	1	(0.1%)	4	(0.6%)
	HEMOPTYSIS	0	.	9	(1.2%)	1	(0.1%)	0	.	10	(1.4%)
	HYPERVENTILATION	0	.	1	(0.1%)	0	.	0	.	1	(0.1%)
	HYPOXIA	0	.	1	(0.1%)	1	(0.1%)	0	.	2	(0.3%)
	LARYNGITIS	0	.	3	(0.4%)	2	(0.3%)	0	.	5	(0.7%)
	PHARYNGITIS	0	.	40	(5.5%)	17	(2.4%)	0	.	57	(7.9%)
	PLEURAL EFFUSION	0	.	0	.	1	(0.1%)	1	(0.1%)	2	(0.3%)
	PLEURAL PAIN	0	.	1	(0.1%)	0	.	1	(0.1%)	2	(0.3%)
	PLEURISY	0	.	1	(0.1%)	0	.	1	(0.1%)	2	(0.3%)
	PNEUMONIA	0	.	1	(0.1%)	11	(1.5%)	12	(1.7%)	24	(3.3%)
	PNEUMONIA LOBAR	0	.	0	.	0	.	1	(0.1%)	1	(0.1%)
	RESPIRATORY DISORDER	0	.	21	(2.9%)	13	(1.8%)	4	(0.6%)	38	(5.3%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM, PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE EVENT FOR EACH PATIENT

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL (N= 723)

WHO BODY SYSTEM	WHO PREFERRED TERM	Missing		Mild		Intensity Moderate		Severe		Total	
RESPIRATORY SYSTEM	RESPIRATORY INSUFFICIENCY	0	.	0	.	1	(0.1%)	2	(0.3%)	3	(0.4%)
	RHINITIS	0	.	61	(8.4%)	10	(1.4%)	1	(0.1%)	72	(10.0%)
	SINUSITIS	0	.	11	(1.5%)	19	(2.6%)	0	.	30	(4.1%)
	SPUTUM INCREASED	0	.	7	(1.0%)	0	.	0	.	7	(1.0%)
	TRACHEITIS	0	.	1	(0.1%)	2	(0.3%)	1	(0.1%)	4	(0.6%)
SKIN AND APPENDAGES	TOTAL	0	.	42	(5.8%)	28	(3.9%)	3	(0.4%)	73	(10.1%)
	ALOPECIA	0	.	0	.	2	(0.3%)	0	.	2	(0.3%)
	ANGIOEDEMA	0	.	1	(0.1%)	0	.	0	.	1	(0.1%)
	BULLOUS ERUPTION	0	.	1	(0.1%)	0	.	0	.	1	(0.1%)
	DERMATITIS	0	.	5	(0.7%)	2	(0.3%)	1	(0.1%)	8	(1.1%)
	DERMATITIS FUNGAL	0	.	1	(0.1%)	1	(0.1%)	0	.	2	(0.3%)
	DERMATITIS LICHENOID	0	.	1	(0.1%)	1	(0.1%)	0	.	2	(0.3%)
	ECZEMA	0	.	7	(1.0%)	2	(0.3%)	0	.	9	(1.2%)
	FOLLICULITIS	0	.	2	(0.3%)	0	.	0	.	2	(0.3%)
	FURUNCULOSIS	0	.	1	(0.1%)	0	.	0	.	1	(0.1%)
	HYPERKERATOSIS	0	.	1	(0.1%)	1	(0.1%)	0	.	2	(0.3%)
	MELANOSIS	0	.	1	(0.1%)	0	.	0	.	1	(0.1%)
	NAIL DISORDER	0	.	1	(0.1%)	0	.	0	.	1	(0.1%)
	PHOTOSENSITIVITY	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	ALLERGIC REACT										
	PRURITUS	0	.	12	(1.7%)	5	(0.7%)	1	(0.1%)	18	(2.5%)
	PSORIASIS	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	RASH	0	.	5	(0.7%)	4	(0.6%)	0	.	9	(1.2%)
	RASH ERYTHEMATOUS	0	.	1	(0.1%)	1	(0.1%)	0	.	2	(0.3%)
	RASH MACULO-PAPULAR	0	.	2	(0.3%)	1	(0.1%)	0	.	3	(0.4%)
	RASH PUSTULAR	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	ROSACEA	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	SKIN DISORDER	0	.	4	(0.6%)	4	(0.6%)	1	(0.1%)	9	(1.2%)
	SKIN DRY	0	.	3	(0.4%)	2	(0.3%)	0	.	5	(0.7%)
	SKIN HYPERTROPHY	0	.	1	(0.1%)	2	(0.3%)	0	.	3	(0.4%)
	SKIN ULCERATION	0	.	3	(0.4%)	1	(0.1%)	0	.	4	(0.6%)
	URTICARIA	0	.	3	(0.4%)	5	(0.7%)	0	.	8	(1.1%)
	VERRUCA	0	.	1	(0.1%)	0	.	0	.	1	(0.1%)
SPECIAL SENSES OTHER	TOTAL	0	.	3	(0.4%)	0	.	0	.	3	(0.4%)
	TASTE PERVERSION	0	.	3	(0.4%)	0	.	0	.	3	(0.4%)
URINARY SYSTEM	TOTAL	0	.	65	(9.0%)	24	(3.3%)	11	(1.5%)	100	(13.8%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM, PREFERRED TERM AND INTENSITY
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3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE EVENT FOR EACH PATIENT

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL (N= 723)

WHO BODY SYSTEM	WHO PREFERRED TERM	Intensity					Total
		Missing	Mild	Moderate	Severe		
URINARY SYSTEM	ALBUMINURIA	0 .	16 (2.2%)	1 (0.1%)	0 .		17 (2.4%)
	BLADDER CALCULUS	0 .	0 .	1 (0.1%)	0 .		1 (0.1%)
	CYSTITIS	0 .	4 (0.6%)	3 (0.4%)	0 .		7 (1.0%)
	DYSURIA	0 .	5 (0.7%)	2 (0.3%)	1 (0.1%)		8 (1.1%)
	HEMATURIA	0 .	20 (2.8%)	5 (0.7%)	1 (0.1%)		26 (3.6%)
	MICTURITION DISORDER	0 .	2 (0.3%)	0 .	0 .		2 (0.3%)
	MICTURITION FREQUENCY	0 .	4 (0.6%)	1 (0.1%)	0 .		5 (0.7%)
	NOCTURIA	0 .	1 (0.1%)	0 .	0 .		1 (0.1%)
	PYELONEPHRITIS	0 .	0 .	0 .	2 (0.3%)		2 (0.3%)
	PYURIA	0 .	14 (1.9%)	2 (0.3%)	0 .		16 (2.2%)
	RENAL CALCULUS	0 .	2 (0.3%)	0 .	0 .		2 (0.3%)
	RENAL CYST	0 .	1 (0.1%)	0 .	0 .		1 (0.1%)
	RENAL FAILURE ACUTE	0 .	0 .	0 .	2 (0.3%)		2 (0.3%)
	RENAL FUNCTION ABNORMAL	0 .	3 (0.4%)	0 .	0 .		3 (0.4%)
	RENAL PAIN	0 .	2 (0.3%)	0 .	1 (0.1%)		3 (0.4%)
	URINARY CASTS	0 .	1 (0.1%)	0 .	0 .		1 (0.1%)
	URINARY INCONTINENCE	0 .	1 (0.1%)	1 (0.1%)	0 .		2 (0.3%)
	URINARY RETENTION	0 .	1 (0.1%)	2 (0.3%)	3 (0.4%)		6 (0.8%)
	URINARY TRACT INFECTION	0 .	17 (2.4%)	13 (1.8%)	2 (0.3%)		32 (4.4%)
	URINE ABNORMAL	0 .	1 (0.1%)	0 .	0 .		1 (0.1%)
VASCULAR EXTRACARDIAC	TOTAL	0 .	14 (1.9%)	15 (2.1%)	3 (0.4%)		32 (4.4%)
	ARTERIOSCLEROSIS	0 .	1 (0.1%)	0 .	0 .		1 (0.1%)
	ARTERITIS	0 .	0 .	1 (0.1%)	0 .		1 (0.1%)
	CEREBROVASCULAR DISORDER	0 .	2 (0.3%)	3 (0.4%)	0 .		5 (0.7%)
	CLAUDICATION INTERMITTENT	0 .	2 (0.3%)	1 (0.1%)	0 .		3 (0.4%)
	CRAMPS LEGS	0 .	2 (0.3%)	2 (0.3%)	0 .		4 (0.6%)
	HEMORRHAGE NOS	0 .	0 .	1 (0.1%)	0 .		1 (0.1%)
	PERIPHERAL ISCHEMIA	0 .	2 (0.3%)	1 (0.1%)	0 .		3 (0.4%)
	PHLEBITIS	0 .	0 .	1 (0.1%)	0 .		1 (0.1%)
	PHLEBITIS SUPERFICIAL	0 .	1 (0.1%)	0 .	0 .		1 (0.1%)
	THROMBOPHLEBITIS DEEP	0 .	0 .	1 (0.1%)	1 (0.1%)		2 (0.3%)
	THROMBOPHLEBITIS LEG	0 .	1 (0.1%)	0 .	0 .		1 (0.1%)
	THROMBOPHLEBITIS	0 .	1 (0.1%)	0 .	0 .		1 (0.1%)
	RETINAL VEIN						

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM, PREFERRED TERM AND INTENSITY
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3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE EVENT FOR EACH PATIENT

TABLE 15.4

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES BY INVESTIGATOR-DETERMINED INTENSITY, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL (N= 723)

WHO BODY SYSTEM	WHO PREFERRED TERM	Missing		Mild		Intensity Moderate		Severe		Total	
VASCULAR EXTRACARDIAC	THROMBOSIS ARTERIAL	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	LEG										
	THROMBOSIS RETINAL	0	.	0	.	2	(0.3%)	0	.	2	(0.3%)
	ARTERY										
	VASCULAR DISORDER	0	.	1	(0.1%)	1	(0.1%)	2	(0.3%)	4	(0.6%)
VISION	VEIN DISORDER	0	.	2	(0.3%)	0	.	0	.	2	(0.3%)
	VEIN VARICOSE	0	.	2	(0.3%)	1	(0.1%)	0	.	3	(0.4%)
	TOTAL	0	.	19	(2.6%)	15	(2.1%)	4	(0.6%)	38	(5.3%)
	BLEPHARITIS	0	.	3	(0.4%)	0	.	0	.	3	(0.4%)
	CATARACT	0	.	5	(0.7%)	5	(0.7%)	2	(0.3%)	12	(1.7%)
WHITE CELL AND RETICULOENDOTHELIAL SYSTE	CONJUNCTIVAL	0	.	0	.	0	.	1	(0.1%)	1	(0.1%)
	HEMORRHAGE										
	CONJUNCTIVITIS	0	.	13	(1.8%)	2	(0.3%)	0	.	15	(2.1%)
	CORNEAL ULCERATION	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	EYE ABNORMALITY	0	.	2	(0.3%)	2	(0.3%)	0	.	4	(0.6%)
	GLAUCOMA	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	MACULA LUTEA	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	DEGENERATION										
	RETINAL DETACHMENT	0	.	0	.	0	.	1	(0.1%)	1	(0.1%)
	RETINAL DISORDER	0	.	1	(0.1%)	1	(0.1%)	0	.	2	(0.3%)
	UVEITIS	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	VISION ABNORMAL	0	.	1	(0.1%)	2	(0.3%)	0	.	3	(0.4%)
	VISUAL FIELD DEFECT	0	.	1	(0.1%)	0	.	0	.	1	(0.1%)
	XEROPHTHALMIA	0	.	2	(0.3%)	0	.	0	.	2	(0.3%)
	TOTAL	0	.	25	(3.5%)	11	(1.5%)	0	.	36	(5.0%)
WHITE CELL AND RETICULOENDOTHELIAL SYSTE	EOSINOPHILIA	0	.	2	(0.3%)	0	.	0	.	2	(0.3%)
	GRANULOCYTOPENIA	0	.	2	(0.3%)	0	.	0	.	2	(0.3%)
	LEUKOCYTOSIS	0	.	17	(2.4%)	6	(0.8%)	0	.	23	(3.2%)
	LEUKOPENIA	0	.	3	(0.4%)	0	.	0	.	3	(0.4%)
	LYMPHADENOPATHY	0	.	2	(0.3%)	3	(0.4%)	0	.	5	(0.7%)
	LYMPHADENOPATHY	0	.	1	(0.1%)	0	.	0	.	1	(0.1%)
	CERVICAL										
	LYMPHANGITIS	0	.	0	.	1	(0.1%)	0	.	1	(0.1%)
	LYMPHEDEMA	0	.	1	(0.1%)	0	.	0	.	1	(0.1%)
	LYMPHOPENIA	0	.	1	(0.1%)	1	(0.1%)	0	.	2	(0.3%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM, PREFERRED TERM AND INTENSITY
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED
3. MAXIMUM INTENSITY IS USED FOR EACH ADVERSE EVENT FOR EACH PATIENT

TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: PLACEBO

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		1		2-7		8-14		15-28	
		(N= 243)		(N= 242)		(N= 237)		(N= 227)	
		n	(%)	n	(%)	n	(%)	n	(%)
TOTAL PATIENTS WITH ADVERSE EXPERIENCES	TOTAL	23	9.5%	78	32.2%	45	19.0%	52	22.9%
BODY AS A WHOLE GENERAL	TOTAL	1	0.4%	8	3.3%	2	0.8%	2	0.9%
	ASTHENIA	0	.	2	0.8%	0	.	0	.
	CHEST PAIN	0	.	0	.	0	.	1	0.4%
	FATIGUE	0	.	3	1.2%	2	0.8%	0	.
	FEVER	0	.	0	.	0	.	0	.
	INJURY	0	.	0	.	0	.	0	.
	MALAISE	1	0.4%	4	1.7%	0	.	0	.
	PAIN	0	.	0	.	0	.	1	0.4%
CARDIOVASCULAR GENERAL	TOTAL	0	.	0	.	0	.	2	0.9%
	HYPERTENSION	0	.	0	.	0	.	2	0.9%
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	TOTAL	4	1.6%	15	6.2%	7	3.0%	2	0.9%
	DIZZINESS	1	0.4%	2	0.8%	2	0.8%	0	.
	HEADACHE	4	1.6%	14	5.8%	3	1.3%	2	0.9%
	NEURALGIA	0	.	0	.	2	0.8%	0	.
	VERTIGO	0	.	0	.	0	.	0	.
GASTROINTESTINAL SYSTEM	TOTAL	13	5.3%	48	19.8%	13	5.5%	14	6.2%
	ABDOMINAL PAIN	6	2.5%	14	5.8%	7	3.0%	5	2.2%
	CONSTIPATION	0	.	0	.	0	.	0	.
	DIARRHEA	2	0.8%	16	6.6%	5	2.1%	4	1.8%
	DYSPEPSIA	1	0.4%	12	5.0%	1	0.4%	2	0.9%
	GASTRITIS	0	.	2	0.8%	0	.	0	.
	GASTROENTERITIS	0	.	2	0.8%	0	.	0	.
	NAUSEA	6	2.5%	10	4.1%	2	0.8%	6	2.6%
	PERIODONTITIS	0	.	0	.	0	.	0	.
	VOMITING	1	0.4%	6	2.5%	2	0.8%	1	0.4%
HEART RATE AND RHYTHM	TOTAL	1	0.4%	0	.	2	0.8%	0	.
	EXTRASYSTOLES	0	.	0	.	0	.	0	.
	TACHYCARDIA	1	0.4%	0	.	2	0.8%	0	.

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM AND PREFERRED TERM

2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS AT EACH TIME INTERVAL

3. ONLY EVENTS OCCURRING IN AT LEAST 2% OF PATIENTS ENROLLED TO SB 207499 ARE INCLUDED

4. EVENTS FOR WHICH THE ONSET IS UNDETERMINED ARE ASSUMED TO HAVE OCCURRED AT DAY 1

TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: PLACEBO

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		29-56		57-84		85-112		113-140	
		(N= 220)		(N= 213)		(N= 207)		(N= 200)	
		n	(%)	n	(%)	n	(%)	n	(%)
TOTAL PATIENTS WITH ADVERSE EXPERIENCES	TOTAL	55	25.0%	52	24.4%	47	22.7%	46	23.0%
BODY AS A WHOLE GENERAL	TOTAL	1	0.5%	3	1.4%	9	4.3%	7	3.5%
	ASTHENIA	1	0.5%	0	.	0	.	3	1.5%
	CHEST PAIN	0	.	2	0.9%	2	1.0%	1	0.5%
	FATIGUE	0	.	0	.	0	.	0	.
	FEVER	0	.	0	.	3	1.4%	1	0.5%
	INJURY	0	.	1	0.5%	3	1.4%	1	0.5%
	MALAISE	0	.	0	.	0	.	1	0.5%
	PAIN	0	.	0	.	1	0.5%	1	0.5%
CARDIOVASCULAR GENERAL	TOTAL	0	.	0	.	2	1.0%	1	0.5%
	HYPERTENSION	0	.	0	.	2	1.0%	1	0.5%
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	TOTAL	2	0.9%	3	1.4%	1	0.5%	0	.
	DIZZINESS	0	.	0	.	1	0.5%	0	.
	HEADACHE	2	0.9%	2	0.9%	0	.	0	.
	NEURALGIA	0	.	1	0.5%	0	.	0	.
	VERTIGO	0	.	0	.	0	.	0	.
GASTROINTESTINAL SYSTEM	TOTAL	11	5.0%	5	2.3%	4	1.9%	7	3.5%
	ABDOMINAL PAIN	4	1.8%	1	0.5%	2	1.0%	1	0.5%
	CONSTIPATION	0	.	0	.	0	.	0	.
	DIARRHEA	5	2.3%	2	0.9%	1	0.5%	2	1.0%
	DYSPEPSIA	2	0.9%	1	0.5%	0	.	1	0.5%
	GASTRITIS	0	.	0	.	1	0.5%	1	0.5%
	GASTROENTERITIS	0	.	0	.	0	.	2	1.0%
	NAUSEA	2	0.9%	1	0.5%	1	0.5%	0	.
	PERIODONTITIS	0	.	0	.	0	.	0	.
	VOMITING	3	1.4%	0	.	1	0.5%	0	.
HEART RATE AND RHYTHM	TOTAL	0	.	0	.	1	0.5%	1	0.5%
	EXTRASYSTOLES	0	.	0	.	1	0.5%	0	.
	TACHYCARDIA	0	.	0	.	0	.	1	0.5%

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TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND
PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: PLACEBO

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		141-168		169-252		253-336		337-420	
		(N= 196)		(N= 194)		(N= 187)		(N= 184)	
		n	(%)	n	(%)	n	(%)	n	(%)
TOTAL PATIENTS WITH ADVERSE EXPERIENCES	TOTAL	44	22.4%	76	39.2%	68	36.4%	59	32.1%
BODY AS A WHOLE GENERAL	TOTAL	5	2.6%	8	4.1%	11	5.9%	5	2.7%
	ASTHENIA	0	.	0	.	0	.	0	.
	CHEST PAIN	1	0.5%	2	1.0%	2	1.1%	1	0.5%
	FATIGUE	0	.	0	.	2	1.1%	0	.
	FEVER	1	0.5%	0	.	1	0.5%	1	0.5%
	INJURY	3	1.5%	2	1.0%	5	2.7%	2	1.1%
	MALAISE	0	.	1	0.5%	2	1.1%	1	0.5%
	PAIN	0	.	3	1.5%	0	.	1	0.5%
CARDIOVASCULAR GENERAL	TOTAL	0	.	1	0.5%	1	0.5%	0	.
	HYPERTENSION	0	.	1	0.5%	1	0.5%	0	.
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	TOTAL	1	0.5%	4	2.1%	6	3.2%	0	.
	DIZZINESS	0	.	0	.	0	.	0	.
	HEADACHE	1	0.5%	2	1.0%	2	1.1%	0	.
	NEURALGIA	0	.	1	0.5%	3	1.6%	0	.
	VERTIGO	0	.	1	0.5%	1	0.5%	0	.
GASTROINTESTINAL SYSTEM	TOTAL	5	2.6%	7	3.6%	7	3.7%	4	2.2%
	ABDOMINAL PAIN	1	0.5%	0	.	3	1.6%	2	1.1%
	CONSTIPATION	0	.	1	0.5%	0	.	0	.
	DIARRHEA	1	0.5%	3	1.5%	0	.	0	.
	DYSPEPSIA	0	.	3	1.5%	1	0.5%	2	1.1%
	GASTRITIS	0	.	0	.	0	.	0	.
	GASTROENTERITIS	0	.	0	.	0	.	0	.
	NAUSEA	2	1.0%	0	.	2	1.1%	0	.
	PERIODONTITIS	1	0.5%	1	0.5%	1	0.5%	0	.
	VOMITING	0	.	0	.	1	0.5%	0	.
HEART RATE AND RHYTHM	TOTAL	1	0.5%	0	.	2	1.1%	3	1.6%
	EXTRASYSTOLES	1	0.5%	0	.	1	0.5%	1	0.5%
	TACHYCARDIA	0	.	0	.	1	0.5%	2	1.1%

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TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: PLACEBO

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		421-504		505-588		589-672		673-756	
		(N= 174)		(N= 171)		(N= 163)		(N= 159)	
		n	(%)	n	(%)	n	(%)	n	(%)
TOTAL PATIENTS WITH ADVERSE EXPERIENCES	TOTAL	61	35.1%	40	23.4%	45	27.6%	29	18.2%
BODY AS A WHOLE GENERAL	TOTAL	7	4.0%	4	2.3%	4	2.5%	3	1.9%
	ASTHENIA	1	0.6%	0	.	1	0.6%	0	.
	CHEST PAIN	2	1.1%	0	.	0	.	1	0.6%
	FATIGUE	1	0.6%	0	.	0	.	0	.
	FEVER	1	0.6%	1	0.6%	1	0.6%	0	.
	INJURY	2	1.1%	3	1.8%	1	0.6%	1	0.6%
	MALAISE	0	.	0	.	0	.	0	.
	PAIN	0	.	0	.	1	0.6%	1	0.6%
CARDIOVASCULAR GENERAL	TOTAL	1	0.6%	0	.	1	0.6%	1	0.6%
	HYPERTENSION	1	0.6%	0	.	1	0.6%	1	0.6%
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	TOTAL	3	1.7%	0	.	1	0.6%	0	.
	DIZZINESS	3	1.7%	0	.	0	.	0	.
	HEADACHE	0	.	0	.	0	.	0	.
	NEURALGIA	0	.	0	.	0	.	0	.
	VERTIGO	0	.	0	.	1	0.6%	0	.
GASTROINTESTINAL SYSTEM	TOTAL	11	6.3%	5	2.9%	6	3.7%	0	.
	ABDOMINAL PAIN	1	0.6%	1	0.6%	1	0.6%	0	.
	CONSTIPATION	2	1.1%	0	.	1	0.6%	0	.
	DIARRHEA	3	1.7%	0	.	0	.	0	.
	DYSPEPSIA	2	1.1%	1	0.6%	1	0.6%	0	.
	GASTRITIS	1	0.6%	1	0.6%	0	.	0	.
	GASTROENTERITIS	2	1.1%	1	0.6%	2	1.2%	0	.
	NAUSEA	0	.	0	.	1	0.6%	0	.
	PERIODONTITIS	1	0.6%	1	0.6%	0	.	0	.
	VOMITING	0	.	0	.	0	.	0	.
HEART RATE AND RHYTHM	TOTAL	1	0.6%	0	.	1	0.6%	0	.
	EXTRASYSTOLES	0	.	0	.	0	.	0	.
	TACHYCARDIA	1	0.6%	0	.	1	0.6%	0	.

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TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: PLACEBO

		DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		757-840 (N= 129)		841-924 (N= 81)		925-1008 (N= 29)		1009-1092 (N= 0)	
WHO BODY SYSTEM	WHO PREFERRED TERM	n	(%)	n	(%)	n	(%)	n	(%)
TOTAL PATIENTS WITH ADVERSE EXPERIENCES	TOTAL	24	18.6%	12	14.8%	1	3.4%	0	.
BODY AS A WHOLE GENERAL	TOTAL	3	2.3%	0	.	0	.	0	.
	ASTHENIA	0	.	0	.	0	.	0	.
	CHEST PAIN	0	.	0	.	0	.	0	.
	FATIGUE	0	.	0	.	0	.	0	.
	FEVER	1	0.8%	0	.	0	.	0	.
	INJURY	2	1.6%	0	.	0	.	0	.
	MALAISE	0	.	0	.	0	.	0	.
	PAIN	0	.	0	.	0	.	0	.
CARDIOVASCULAR GENERAL	TOTAL	0	.	0	.	0	.	0	.
	HYPERTENSION	0	.	0	.	0	.	0	.
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	TOTAL	1	0.8%	0	.	1	3.4%	0	.
	DIZZINESS	0	.	0	.	0	.	0	.
	HEADACHE	0	.	0	.	0	.	0	.
	NEURALGIA	0	.	0	.	0	.	0	.
	VERTIGO	1	0.8%	0	.	1	3.4%	0	.
GASTROINTESTINAL SYSTEM	TOTAL	4	3.1%	1	1.2%	0	.	0	.
	ABDOMINAL PAIN	1	0.8%	0	.	0	.	0	.
	CONSTIPATION	1	0.8%	0	.	0	.	0	.
	DIARRHEA	0	.	0	.	0	.	0	.
	DYSPEPSIA	0	.	0	.	0	.	0	.
	GASTRITIS	0	.	0	.	0	.	0	.
	GASTROENTERITIS	1	0.8%	1	1.2%	0	.	0	.
	NAUSEA	1	0.8%	0	.	0	.	0	.
	PERIODONTITIS	0	.	0	.	0	.	0	.
	VOMITING	0	.	0	.	0	.	0	.
HEART RATE AND RHYTHM	TOTAL	0	.	1	1.2%	0	.	0	.
	EXTRASYSTOLES	0	.	0	.	0	.	0	.
	TACHYCARDIA	0	.	1	1.2%	0	.	0	.

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TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: PLACEBO

		DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE			
		1093-1176 (N= 0)		TOTAL (N= 243)	
WHO BODY SYSTEM	WHO PREFERRED TERM	n	(%)	n	(%)
TOTAL PATIENTS WITH ADVERSE EXPERIENCES	TOTAL	0	.	229	94.2%
BODY AS A WHOLE GENERAL	TOTAL	0	.	65	26.7%
	ASTHENIA	0	.	8	3.3%
	CHEST PAIN	0	.	15	6.2%
	FATIGUE	0	.	8	3.3%
	FEVER	0	.	11	4.5%
	INJURY	0	.	26	10.7%
	MALAISE	0	.	10	4.1%
	PAIN	0	.	9	3.7%
CARDIOVASCULAR GENERAL	TOTAL	0	.	10	4.1%
	HYPERTENSION	0	.	10	4.1%
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	TOTAL	0	.	48	19.8%
	DIZZINESS	0	.	9	3.7%
	HEADACHE	0	.	32	13.2%
	NEURALGIA	0	.	7	2.9%
	VERTIGO	0	.	5	2.1%
GASTROINTESTINAL SYSTEM	TOTAL	0	.	122	50.2%
	ABDOMINAL PAIN	0	.	50	20.6%
	CONSTIPATION	0	.	5	2.1%
	DIARRHEA	0	.	44	18.1%
	DYSPEPSIA	0	.	30	12.3%
	GASTRITIS	0	.	6	2.5%
	GASTROENTERITIS	0	.	11	4.5%
	NAUSEA	0	.	34	14.0%
	PERIODONTITIS	0	.	5	2.1%
	VOMITING	0	.	15	6.2%
HEART RATE AND RHYTHM	TOTAL	0	.	14	5.8%
	EXTRASYSTOLES	0	.	4	1.6%
	TACHYCARDIA	0	.	10	4.1%

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INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: PLACEBO

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		1		2-7		8-14		15-28	
		(N= 243)		(N= 242)		(N= 237)		(N= 227)	
		n	(%)	n	(%)	n	(%)	n	(%)
LIVER AND BILIARY SYSTEM	TOTAL	0	.	0	.	1	0.4%	1	0.4%
	GAMMA-GT INCREASED	0	.	0	.	0	.	1	0.4%
	HEPATIC ENZYMES INCREASED	0	.	0	.	1	0.4%	0	.
METABOLIC AND NUTRITIONAL	TOTAL	1	0.4%	1	0.4%	1	0.4%	1	0.4%
	HYPERGLYCEMIA	1	0.4%	0	.	1	0.4%	1	0.4%
	WEIGHT DECREASE	0	.	1	0.4%	0	.	0	.
MUSCULOSKELETAL SYSTEM	TOTAL	0	.	1	0.4%	1	0.4%	4	1.8%
	ARTHRALGIA	0	.	0	.	0	.	3	1.3%
	ARTHRITIS	0	.	0	.	0	.	0	.
	BACK PAIN	0	.	1	0.4%	1	0.4%	1	0.4%
	MYALGIA	0	.	0	.	0	.	0	.
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	TOTAL	0	.	0	.	1	0.4%	0	.
	ANGINA PECTORIS	0	.	0	.	1	0.4%	0	.
NEOPLASM	TOTAL	0	.	0	.	0	.	0	.
	NEOPLASM NOS	0	.	0	.	0	.	0	.
PSYCHIATRIC	TOTAL	1	0.4%	0	.	0	.	3	1.3%
	ANXIETY	0	.	0	.	0	.	1	0.4%
	DEPRESSION	0	.	0	.	0	.	0	.
	INSOMNIA	1	0.4%	0	.	0	.	2	0.9%
REPRODUCTIVE MALE	TOTAL	0	.	1	0.4%	0	.	0	.
	PROSTATIC DISORDER	0	.	1	0.4%	0	.	0	.
RESISTANCE MECHANISM	TOTAL	0	.	1	0.4%	1	0.4%	1	0.4%
	INFECTION	0	.	0	.	0	.	0	.
	INFECTION VIRAL	0	.	1	0.4%	0	.	0	.
	UPPER RESP TRACT INFECTION	0	.	0	.	1	0.4%	1	0.4%
RESPIRATORY SYSTEM	TOTAL	0	.	8	3.3%	9	3.8%	23	10.1%
	BRONCHITIS	0	.	0	.	1	0.4%	0	.

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INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: PLACEBO

		DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		29-56 (N= 220)		57-84 (N= 213)		85-112 (N= 207)		113-140 (N= 200)	
WHO BODY SYSTEM	WHO PREFERRED TERM	n	(%)	n	(%)	n	(%)	n	(%)
LIVER AND BILIARY SYSTEM	TOTAL	0	.	0	.	2	1.0%	1	0.5%
	GAMMA-GT INCREASED	0	.	0	.	1	0.5%	1	0.5%
	HEPATIC ENZYMES INCREASED	0	.	0	.	1	0.5%	0	.
METABOLIC AND NUTRITIONAL	TOTAL	1	0.5%	1	0.5%	1	0.5%	1	0.5%
	HYPERGLYCEMIA	0	.	1	0.5%	1	0.5%	1	0.5%
	WEIGHT DECREASE	1	0.5%	0	.	0	.	0	.
MUSCULOSKELETAL SYSTEM	TOTAL	3	1.4%	2	0.9%	2	1.0%	3	1.5%
	ARTHRALGIA	2	0.9%	1	0.5%	1	0.5%	0	.
	ARTHRITIS	0	.	0	.	0	.	1	0.5%
	BACK PAIN	2	0.9%	1	0.5%	1	0.5%	1	0.5%
	MYALGIA	0	.	0	.	0	.	1	0.5%
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	TOTAL	1	0.5%	1	0.5%	0	.	0	.
	ANGINA PECTORIS	1	0.5%	1	0.5%	0	.	0	.
NEOPLASM	TOTAL	0	.	0	.	0	.	0	.
	NEOPLASM NOS	0	.	0	.	0	.	0	.
PSYCHIATRIC	TOTAL	5	2.3%	5	2.3%	2	1.0%	0	.
	ANXIETY	2	0.9%	3	1.4%	2	1.0%	0	.
	DEPRESSION	2	0.9%	0	.	0	.	0	.
	INSOMNIA	1	0.5%	2	0.9%	0	.	0	.
REPRODUCTIVE MALE	TOTAL	0	.	0	.	1	0.5%	1	0.5%
	PROSTATIC DISORDER	0	.	0	.	1	0.5%	1	0.5%
RESISTANCE MECHANISM	TOTAL	6	2.7%	6	2.8%	4	1.9%	5	2.5%
	INFECTION	2	0.9%	0	.	0	.	0	.
	INFECTION VIRAL	4	1.8%	4	1.9%	2	1.0%	4	2.0%
	UPPER RESP TRACT INFECTION	1	0.5%	2	0.9%	2	1.0%	1	0.5%
RESPIRATORY SYSTEM	TOTAL	20	9.1%	23	10.8%	15	7.2%	17	8.5%
	BRONCHITIS	0	.	0	.	0	.	1	0.5%

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4. EVENTS FOR WHICH THE ONSET IS UNDETERMINED ARE ASSUMED TO HAVE OCCURRED AT DAY 1

TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: PLACEBO

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		141-168		169-252		253-336		337-420	
		(N= 196)		(N= 194)		(N= 187)		(N= 184)	
		n	(%)	n	(%)	n	(%)	n	(%)
LIVER AND BILIARY SYSTEM	TOTAL	0	.	0	.	1	0.5%	0	.
	GAMMA-GT INCREASED	0	.	0	.	0	.	0	.
	HEPATIC ENZYMES INCREASED	0	.	0	.	1	0.5%	0	.
METABOLIC AND NUTRITIONAL	TOTAL	1	0.5%	1	0.5%	1	0.5%	0	.
	HYPERGLYCEMIA	1	0.5%	1	0.5%	0	.	0	.
	WEIGHT DECREASE	0	.	0	.	1	0.5%	0	.
MUSCULOSKELETAL SYSTEM	TOTAL	1	0.5%	8	4.1%	8	4.3%	5	2.7%
	ARTHRALGIA	0	.	2	1.0%	2	1.1%	2	1.1%
	ARTHRITIS	0	.	0	.	3	1.6%	0	.
	BACK PAIN	1	0.5%	2	1.0%	2	1.1%	2	1.1%
	MYALGIA	0	.	4	2.1%	1	0.5%	1	0.5%
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	TOTAL	0	.	2	1.0%	0	.	0	.
	ANGINA PECTORIS	0	.	2	1.0%	0	.	0	.
NEOPLASM	TOTAL	0	.	4	2.1%	0	.	2	1.1%
	NEOPLASM NOS	0	.	4	2.1%	0	.	2	1.1%
PSYCHIATRIC	TOTAL	4	2.0%	0	.	2	1.1%	2	1.1%
	ANXIETY	1	0.5%	0	.	1	0.5%	1	0.5%
	DEPRESSION	3	1.5%	0	.	1	0.5%	0	.
	INSOMNIA	0	.	0	.	0	.	1	0.5%
REPRODUCTIVE MALE	TOTAL	0	.	2	1.0%	2	1.1%	1	0.5%
	PROSTATIC DISORDER	0	.	2	1.0%	2	1.1%	1	0.5%
RESISTANCE MECHANISM	TOTAL	1	0.5%	3	1.5%	3	1.6%	6	3.3%
	INFECTION	0	.	1	0.5%	1	0.5%	1	0.5%
	INFECTION VIRAL	1	0.5%	1	0.5%	1	0.5%	2	1.1%
	UPPER RESP TRACT INFECTION	0	.	1	0.5%	2	1.1%	3	1.6%
RESPIRATORY SYSTEM	TOTAL	12	6.1%	32	16.5%	25	13.4%	18	9.8%
	BRONCHITIS	0	.	0	.	0	.	1	0.5%

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TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: PLACEBO

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		421-504 (N= 174)		505-588 (N= 171)		589-672 (N= 163)		673-756 (N= 159)	
		n	(%)	n	(%)	n	(%)	n	(%)
LIVER AND BILIARY SYSTEM	TOTAL	2	1.1%	1	0.6%	0	.	0	.
	GAMMA-GT INCREASED	2	1.1%	1	0.6%	0	.	0	.
	HEPATIC ENZYMES INCREASED	0	.	0	.	0	.	0	.
METABOLIC AND NUTRITIONAL	TOTAL	3	1.7%	1	0.6%	0	.	2	1.3%
	HYPERGLYCEMIA	0	.	0	.	0	.	0	.
	WEIGHT DECREASE	3	1.7%	1	0.6%	0	.	2	1.3%
MUSCULOSKELETAL SYSTEM	TOTAL	8	4.6%	3	1.8%	5	3.1%	3	1.9%
	ARTHRALGIA	3	1.7%	2	1.2%	0	.	0	.
	ARTHRITIS	0	.	0	.	1	0.6%	1	0.6%
	BACK PAIN	4	2.3%	1	0.6%	2	1.2%	0	.
	MYALGIA	2	1.1%	0	.	2	1.2%	2	1.3%
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	TOTAL	1	0.6%	0	.	1	0.6%	0	.
	ANGINA PECTORIS	1	0.6%	0	.	1	0.6%	0	.
NEOPLASM	TOTAL	1	0.6%	0	.	1	0.6%	1	0.6%
	NEOPLASM NOS	1	0.6%	0	.	1	0.6%	1	0.6%
PSYCHIATRIC	TOTAL	3	1.7%	0	.	4	2.5%	0	.
	ANXIETY	1	0.6%	0	.	1	0.6%	0	.
	DEPRESSION	2	1.1%	0	.	2	1.2%	0	.
	INSOMNIA	0	.	0	.	1	0.6%	0	.
REPRODUCTIVE MALE	TOTAL	1	0.6%	1	0.6%	0	.	0	.
	PROSTATIC DISORDER	1	0.6%	1	0.6%	0	.	0	.
RESISTANCE MECHANISM	TOTAL	4	2.3%	1	0.6%	2	1.2%	0	.
	INFECTION	0	.	0	.	1	0.6%	0	.
	INFECTION VIRAL	1	0.6%	0	.	0	.	0	.
	UPPER RESP TRACT INFECTION	3	1.7%	1	0.6%	1	0.6%	0	.
RESPIRATORY SYSTEM	TOTAL	18	10.3%	10	5.8%	3	1.8%	5	3.1%
	BRONCHITIS	2	1.1%	0	.	0	.	1	0.6%

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INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: PLACEBO

		DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		757-840 (N= 129)		841-924 (N= 81)		925-1008 (N= 29)		1009-1092 (N= 0)	
WHO BODY SYSTEM	WHO PREFERRED TERM	n	(%)	n	(%)	n	(%)	n	(%)
LIVER AND BILIARY SYSTEM	TOTAL	0	.	1	1.2%	0	.	0	.
	GAMMA-GT INCREASED	0	.	1	1.2%	0	.	0	.
	HEPATIC ENZYMES INCREASED	0	.	0	.	0	.	0	.
METABOLIC AND NUTRITIONAL	TOTAL	0	.	0	.	0	.	0	.
	HYPERGLYCEMIA	0	.	0	.	0	.	0	.
	WEIGHT DECREASE	0	.	0	.	0	.	0	.
MUSCULOSKELETAL SYSTEM	TOTAL	2	1.6%	1	1.2%	0	.	0	.
	ARTHRALGIA	1	0.8%	1	1.2%	0	.	0	.
	ARTHRITIS	1	0.8%	0	.	0	.	0	.
	BACK PAIN	1	0.8%	0	.	0	.	0	.
	MYALGIA	0	.	0	.	0	.	0	.
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	TOTAL	0	.	0	.	0	.	0	.
	ANGINA PECTORIS	0	.	0	.	0	.	0	.
NEOPLASM	TOTAL	0	.	1	1.2%	0	.	0	.
	NEOPLASM NOS	0	.	1	1.2%	0	.	0	.
PSYCHIATRIC	TOTAL	0	.	0	.	0	.	0	.
	ANXIETY	0	.	0	.	0	.	0	.
	DEPRESSION	0	.	0	.	0	.	0	.
	INSOMNIA	0	.	0	.	0	.	0	.
REPRODUCTIVE MALE	TOTAL	1	0.8%	0	.	0	.	0	.
	PROSTATIC DISORDER	1	0.8%	0	.	0	.	0	.
RESISTANCE MECHANISM	TOTAL	1	0.8%	0	.	0	.	0	.
	INFECTION	0	.	0	.	0	.	0	.
	INFECTION VIRAL	0	.	0	.	0	.	0	.
	UPPER RESP TRACT INFECTION	1	0.8%	0	.	0	.	0	.
RESPIRATORY SYSTEM	TOTAL	9	7.0%	3	3.7%	0	.	0	.
	BRONCHITIS	2	1.6%	0	.	0	.	0	.

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TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: PLACEBO

		DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE			
		1093-1176 (N= 0)		TOTAL (N= 243)	
WHO BODY SYSTEM	WHO PREFERRED TERM	n	(%)	n	(%)
LIVER AND BILIARY SYSTEM	TOTAL	0	.	9	3.7%
	GAMMA-GT INCREASED	0	.	7	2.9%
	HEPATIC ENZYMES INCREASED	0	.	3	1.2%
METABOLIC AND NUTRITIONAL	TOTAL	0	.	17	7.0%
	HYPERGLYCEMIA	0	.	8	3.3%
	WEIGHT DECREASE	0	.	9	3.7%
MUSCULOSKELETAL SYSTEM	TOTAL	0	.	51	21.0%
	ARTHRALGIA	0	.	20	8.2%
	ARTHRITIS	0	.	7	2.9%
	BACK PAIN	0	.	23	9.5%
	MYALGIA	0	.	13	5.3%
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	TOTAL	0	.	7	2.9%
	ANGINA PECTORIS	0	.	7	2.9%
NEOPLASM	TOTAL	0	.	10	4.1%
	NEOPLASM NOS	0	.	10	4.1%
PSYCHIATRIC	TOTAL	0	.	27	11.1%
	ANXIETY	0	.	13	5.3%
	DEPRESSION	0	.	10	4.1%
	INSOMNIA	0	.	8	3.3%
REPRODUCTIVE MALE	TOTAL	0	.	11	4.5%
	PROSTATIC DISORDER	0	.	11	4.5%
RESISTANCE MECHANISM	TOTAL	0	.	41	16.9%
	INFECTION	0	.	6	2.5%
	INFECTION VIRAL	0	.	21	8.6%
	UPPER RESP TRACT INFECTION	0	.	20	8.2%
RESPIRATORY SYSTEM	TOTAL	0	.	170	70.0%
	BRONCHITIS	0	.	8	3.3%

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TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: PLACEBO

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		1		2-7		8-14		15-28	
		(N= 243)		(N= 242)		(N= 237)		(N= 227)	
		n	(%)	n	(%)	n	(%)	n	(%)
RESPIRATORY SYSTEM	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	0	.	5	2.1%	4	1.7%	15	6.6%
	COUGHING	0	.	1	0.4%	0	.	2	0.9%
	DYSPNEA	0	.	0	.	0	.	2	0.9%
	PHARYNGITIS	0	.	1	0.4%	1	0.4%	0	.
	PNEUMONIA	0	.	0	.	0	.	0	.
	RESPIRATORY DISORDER	0	.	0	.	0	.	2	0.9%
	RHINITIS	0	.	1	0.4%	2	0.8%	2	0.9%
	SINUSITIS	0	.	0	.	1	0.4%	2	0.9%
SKIN AND APPENDAGES	TOTAL	0	.	0	.	0	.	1	0.4%
	PRURITUS	0	.	0	.	0	.	1	0.4%
URINARY SYSTEM	TOTAL	0	.	2	0.8%	2	0.8%	0	.
	ALBUMINURIA	0	.	0	.	1	0.4%	0	.
	HEMATURIA	0	.	2	0.8%	1	0.4%	0	.
	PYURIA	0	.	1	0.4%	0	.	0	.
	URINARY TRACT INFECTION	0	.	0	.	0	.	0	.
VISION	TOTAL	0	.	0	.	0	.	1	0.4%
	CONJUNCTIVITIS	0	.	0	.	0	.	1	0.4%
WHITE CELL AND RETICULOENDOTHELIAL SYSTE	TOTAL	0	.	0	.	0	.	1	0.4%
	LEUKOCYTOSIS	0	.	0	.	0	.	1	0.4%

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INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: PLACEBO

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		29-56 (N= 220)		57-84 (N= 213)		85-112 (N= 207)		113-140 (N= 200)	
		n	(%)	n	(%)	n	(%)	n	(%)
RESPIRATORY SYSTEM	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	17	7.7%	19	8.9%	11	5.3%	12	6.0%
	COUGHING	1	0.5%	0	.	1	0.5%	1	0.5%
	DYSPNEA	0	.	1	0.5%	0	.	0	.
	PHARYNGITIS	1	0.5%	1	0.5%	0	.	1	0.5%
	PNEUMONIA	0	.	1	0.5%	2	1.0%	0	.
	RESPIRATORY DISORDER	1	0.5%	0	.	0	.	1	0.5%
	RHINITIS	2	0.9%	1	0.5%	1	0.5%	2	1.0%
	SINUSITIS	0	.	0	.	0	.	0	.
SKIN AND APPENDAGES	TOTAL	1	0.5%	0	.	0	.	1	0.5%
	PRURITUS	1	0.5%	0	.	0	.	1	0.5%
URINARY SYSTEM	TOTAL	2	0.9%	2	0.9%	2	1.0%	0	.
	ALBUMINURIA	0	.	0	.	0	.	0	.
	HEMATURIA	1	0.5%	1	0.5%	1	0.5%	0	.
	PYURIA	0	.	1	0.5%	1	0.5%	0	.
	URINARY TRACT INFECTION	1	0.5%	0	.	0	.	0	.
VISION	TOTAL	0	.	0	.	0	.	0	.
	CONJUNCTIVITIS	0	.	0	.	0	.	0	.
WHITE CELL AND RETICULOENDOTHELIAL SYSTE	TOTAL	0	.	1	0.5%	0	.	0	.
	LEUKOCYTOSIS	0	.	1	0.5%	0	.	0	.

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PROTOCOL 040

PRIOR TREATMENT: PLACEBO

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		141-168		169-252		253-336		337-420	
		(N= 196)		(N= 194)		(N= 187)		(N= 184)	
		n	(%)	n	(%)	n	(%)	n	(%)
RESPIRATORY SYSTEM	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	8	4.1%	21	10.8%	16	8.6%	10	5.4%
	COUGHING	0	.	2	1.0%	1	0.5%	0	.
	DYSPNEA	0	.	1	0.5%	1	0.5%	1	0.5%
	PHARYNGITIS	0	.	1	0.5%	2	1.1%	2	1.1%
	PNEUMONIA	1	0.5%	0	.	0	.	2	1.1%
	RESPIRATORY DISORDER	0	.	0	.	3	1.6%	1	0.5%
	RHINITIS	3	1.5%	6	3.1%	3	1.6%	1	0.5%
	SINUSITIS	0	.	3	1.5%	2	1.1%	1	0.5%
SKIN AND APPENDAGES	TOTAL	0	.	1	0.5%	0	.	0	.
	PRURITUS	0	.	1	0.5%	0	.	0	.
URINARY SYSTEM	TOTAL	2	1.0%	5	2.6%	2	1.1%	2	1.1%
	ALBUMINURIA	2	1.0%	0	.	1	0.5%	0	.
	HEMATURIA	0	.	1	0.5%	1	0.5%	0	.
	PYURIA	0	.	0	.	0	.	0	.
	URINARY TRACT INFECTION	0	.	4	2.1%	0	.	2	1.1%
VISION	TOTAL	0	.	1	0.5%	1	0.5%	0	.
	CONJUNCTIVITIS	0	.	1	0.5%	1	0.5%	0	.
WHITE CELL AND RETICULOENDOTHELIAL SYSTE	TOTAL	0	.	1	0.5%	1	0.5%	0	.
	LEUKOCYTOSIS	0	.	1	0.5%	1	0.5%	0	.

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PROTOCOL 040

PRIOR TREATMENT: PLACEBO

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		421-504 (N= 174)		505-588 (N= 171)		589-672 (N= 163)		673-756 (N= 159)	
		n	(%)	n	(%)	n	(%)	n	(%)
RESPIRATORY SYSTEM	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	8	4.6%	4	2.3%	1	0.6%	1	0.6%
	COUGHING	3	1.7%	1	0.6%	0	.	0	.
	DYSPNEA	0	.	1	0.6%	0	.	0	.
	PHARYNGITIS	1	0.6%	2	1.2%	0	.	1	0.6%
	PNEUMONIA	1	0.6%	0	.	0	.	2	1.3%
	RESPIRATORY DISORDER	1	0.6%	0	.	1	0.6%	0	.
	RHINITIS	0	.	1	0.6%	1	0.6%	0	.
	SINUSITIS	2	1.1%	1	0.6%	0	.	0	.
SKIN AND APPENDAGES	TOTAL	0	.	0	.	0	.	0	.
	PRURITUS	0	.	0	.	0	.	0	.
URINARY SYSTEM	TOTAL	3	1.7%	2	1.2%	1	0.6%	2	1.3%
	ALBUMINURIA	1	0.6%	0	.	0	.	0	.
	HEMATURIA	1	0.6%	2	1.2%	1	0.6%	0	.
	PYURIA	0	.	0	.	0	.	1	0.6%
	URINARY TRACT INFECTION	2	1.1%	0	.	0	.	1	0.6%
VISION	TOTAL	1	0.6%	1	0.6%	1	0.6%	0	.
	CONJUNCTIVITIS	1	0.6%	1	0.6%	1	0.6%	0	.
WHITE CELL AND RETICULOENDOTHELIAL SYSTE	TOTAL	1	0.6%	0	.	0	.	1	0.6%
	LEUKOCYTOSIS	1	0.6%	0	.	0	.	1	0.6%

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4. EVENTS FOR WHICH THE ONSET IS UNDETERMINED ARE ASSUMED TO HAVE OCCURRED AT DAY 1

TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: PLACEBO

		DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		757-840 (N= 129)		841-924 (N= 81)		925-1008 (N= 29)		1009-1092 (N= 0)	
WHO BODY SYSTEM	WHO PREFERRED TERM	n	(%)	n	(%)	n	(%)	n	(%)
RESPIRATORY SYSTEM	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	2	1.6%	1	1.2%	0	.	0	.
	COUGHING	0	.	0	.	0	.	0	.
	DYSPNEA	1	0.8%	0	.	0	.	0	.
	PHARYNGITIS	1	0.8%	0	.	0	.	0	.
	PNEUMONIA	1	0.8%	0	.	0	.	0	.
	RESPIRATORY DISORDER	0	.	0	.	0	.	0	.
	RHINITIS	1	0.8%	1	1.2%	0	.	0	.
	SINUSITIS	1	0.8%	1	1.2%	0	.	0	.
SKIN AND APPENDAGES	TOTAL	0	.	0	.	0	.	0	.
	PRURITUS	0	.	0	.	0	.	0	.
URINARY SYSTEM	TOTAL	0	.	1	1.2%	0	.	0	.
	ALBUMINURIA	0	.	0	.	0	.	0	.
	HEMATURIA	0	.	1	1.2%	0	.	0	.
	PYURIA	0	.	0	.	0	.	0	.
	URINARY TRACT INFECTION	0	.	0	.	0	.	0	.
VISION	TOTAL	1	0.8%	0	.	0	.	0	.
	CONJUNCTIVITIS	1	0.8%	0	.	0	.	0	.
WHITE CELL AND RETICULOENDOTHELIAL SYSTE	TOTAL	0	.	0	.	0	.	0	.
	LEUKOCYTOSIS	0	.	0	.	0	.	0	.

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM AND PREFERRED TERM
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TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: PLACEBO

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE			
		1093-1176 (N= 0)		TOTAL (N= 243)	
		n	(%)	n	(%)
RESPIRATORY SYSTEM	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	0	.	155	63.8%
	COUGHING	0	.	13	5.3%
	DYSPNEA	0	.	8	3.3%
	PHARYNGITIS	0	.	15	6.2%
	PNEUMONIA	0	.	10	4.1%
	RESPIRATORY DISORDER	0	.	10	4.1%
	RHINITIS	0	.	28	11.5%
	SINUSITIS	0	.	14	5.8%
SKIN AND APPENDAGES	TOTAL	0	.	4	1.6%
	PRURITUS	0	.	4	1.6%
URINARY SYSTEM	TOTAL	0	.	25	10.3%
	ALBUMINURIA	0	.	5	2.1%
	HEMATURIA	0	.	13	5.3%
	PYURIA	0	.	4	1.6%
	URINARY TRACT INFECTION	0	.	10	4.1%
VISION	TOTAL	0	.	7	2.9%
	CONJUNCTIVITIS	0	.	7	2.9%
WHITE CELL AND RETICULOENDOTHELIAL SYSTE	TOTAL	0	.	6	2.5%
	LEUKOCYTOSIS	0	.	6	2.5%

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TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		1		2-7		8-14		15-28	
		(N= 480)		(N= 479)		(N= 468)		(N= 465)	
		n	(%)	n	(%)	n	(%)	n	(%)
TOTAL PATIENTS WITH ADVERSE EXPERIENCES	TOTAL	23	4.8%	88	18.4%	71	15.2%	91	19.6%
BODY AS A WHOLE GENERAL	TOTAL	1	0.2%	3	0.6%	5	1.1%	6	1.3%
	ASTHENIA	0	.	1	0.2%	1	0.2%	0	.
	CHEST PAIN	0	.	0	.	0	.	1	0.2%
	FATIGUE	0	.	1	0.2%	1	0.2%	0	.
	FEVER	0	.	1	0.2%	2	0.4%	1	0.2%
	INJURY	0	.	0	.	1	0.2%	2	0.4%
	MALAISE	1	0.2%	0	.	0	.	0	.
	PAIN	0	.	1	0.2%	1	0.2%	2	0.4%
CARDIOVASCULAR GENERAL	TOTAL	0	.	0	.	1	0.2%	2	0.4%
	HYPERTENSION	0	.	0	.	1	0.2%	2	0.4%
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	TOTAL	2	0.4%	13	2.7%	6	1.3%	5	1.1%
	DIZZINESS	1	0.2%	3	0.6%	3	0.6%	1	0.2%
	HEADACHE	1	0.2%	10	2.1%	3	0.6%	3	0.6%
	NEURALGIA	0	.	0	.	0	.	1	0.2%
	VERTIGO	0	.	0	.	0	.	0	.
GASTROINTESTINAL SYSTEM	TOTAL	10	2.1%	39	8.1%	16	3.4%	14	3.0%
	ABDOMINAL PAIN	1	0.2%	10	2.1%	4	0.9%	6	1.3%
	CONSTIPATION	1	0.2%	1	0.2%	0	.	1	0.2%
	DIARRHEA	2	0.4%	11	2.3%	6	1.3%	2	0.4%
	DYSPEPSIA	1	0.2%	6	1.3%	2	0.4%	4	0.9%
	GASTRITIS	2	0.4%	1	0.2%	0	.	0	.
	GASTROENTERITIS	0	.	2	0.4%	0	.	0	.
	NAUSEA	3	0.6%	8	1.7%	3	0.6%	2	0.4%
	PERIODONTITIS	0	.	1	0.2%	1	0.2%	1	0.2%
	VOMITING	0	.	2	0.4%	0	.	1	0.2%
HEART RATE AND RHYTHM	TOTAL	1	0.2%	1	0.2%	0	.	0	.
	EXTRASYSTOLES	0	.	1	0.2%	0	.	0	.
	TACHYCARDIA	1	0.2%	0	.	0	.	0	.

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TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		29-56 (N= 459)		57-84 (N= 451)		85-112 (N= 444)		113-140 (N= 438)	
		n	(%)	n	(%)	n	(%)	n	(%)
TOTAL PATIENTS WITH ADVERSE EXPERIENCES	TOTAL	112	24.4%	111	24.6%	93	20.9%	94	21.5%
BODY AS A WHOLE GENERAL	TOTAL	7	1.5%	13	2.9%	6	1.4%	4	0.9%
	ASTHENIA	2	0.4%	0	.	1	0.2%	0	.
	CHEST PAIN	2	0.4%	3	0.7%	0	.	0	.
	FATIGUE	0	.	0	.	0	.	0	.
	FEVER	0	.	2	0.4%	0	.	1	0.2%
	INJURY	2	0.4%	6	1.3%	2	0.5%	2	0.5%
	MALAISE	1	0.2%	1	0.2%	1	0.2%	0	.
	PAIN	1	0.2%	1	0.2%	2	0.5%	1	0.2%
CARDIOVASCULAR GENERAL	TOTAL	1	0.2%	2	0.4%	0	.	1	0.2%
	HYPERTENSION	1	0.2%	2	0.4%	0	.	1	0.2%
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	TOTAL	10	2.2%	5	1.1%	1	0.2%	3	0.7%
	DIZZINESS	4	0.9%	0	.	0	.	0	.
	HEADACHE	5	1.1%	3	0.7%	1	0.2%	1	0.2%
	NEURALGIA	1	0.2%	1	0.2%	0	.	1	0.2%
	VERTIGO	0	.	1	0.2%	0	.	1	0.2%
GASTROINTESTINAL SYSTEM	TOTAL	11	2.4%	19	4.2%	11	2.5%	13	3.0%
	ABDOMINAL PAIN	4	0.9%	7	1.6%	0	.	6	1.4%
	CONSTIPATION	0	.	0	.	0	.	0	.
	DIARRHEA	4	0.9%	5	1.1%	4	0.9%	2	0.5%
	DYSPEPSIA	1	0.2%	3	0.7%	3	0.7%	3	0.7%
	GASTRITIS	1	0.2%	0	.	1	0.2%	0	.
	GASTROENTERITIS	0	.	2	0.4%	0	.	1	0.2%
	NAUSEA	1	0.2%	2	0.4%	1	0.2%	2	0.5%
	PERIODONTITIS	1	0.2%	0	.	1	0.2%	0	.
	VOMITING	0	.	0	.	1	0.2%	2	0.5%
HEART RATE AND RHYTHM	TOTAL	1	0.2%	4	0.9%	1	0.2%	3	0.7%
	EXTRASYSTOLES	0	.	3	0.7%	1	0.2%	2	0.5%
	TACHYCARDIA	1	0.2%	1	0.2%	0	.	1	0.2%

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INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		141-168		169-252		253-336		337-420	
		(N= 435)		(N= 431)		(N= 413)		(N= 402)	
		n	(%)	n	(%)	n	(%)	n	(%)
TOTAL PATIENTS WITH ADVERSE EXPERIENCES	TOTAL	83	19.1%	161	37.4%	137	33.2%	123	30.6%
BODY AS A WHOLE GENERAL	TOTAL	10	2.3%	11	2.6%	15	3.6%	20	5.0%
	ASTHENIA	0	.	1	0.2%	0	.	4	1.0%
	CHEST PAIN	1	0.2%	1	0.2%	6	1.5%	3	0.7%
	FATIGUE	1	0.2%	1	0.2%	2	0.5%	2	0.5%
	FEVER	0	.	0	.	0	.	0	.
	INJURY	7	1.6%	7	1.6%	5	1.2%	10	2.5%
	MALAISE	0	.	0	.	0	.	1	0.2%
	PAIN	1	0.2%	2	0.5%	3	0.7%	1	0.2%
CARDIOVASCULAR GENERAL	TOTAL	1	0.2%	5	1.2%	5	1.2%	4	1.0%
	HYPERTENSION	1	0.2%	5	1.2%	5	1.2%	4	1.0%
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	TOTAL	1	0.2%	10	2.3%	11	2.7%	6	1.5%
	DIZZINESS	0	.	3	0.7%	3	0.7%	2	0.5%
	HEADACHE	1	0.2%	4	0.9%	4	1.0%	2	0.5%
	NEURALGIA	0	.	1	0.2%	2	0.5%	2	0.5%
	VERTIGO	0	.	2	0.5%	2	0.5%	1	0.2%
GASTROINTESTINAL SYSTEM	TOTAL	4	0.9%	21	4.9%	26	6.3%	7	1.7%
	ABDOMINAL PAIN	2	0.5%	6	1.4%	3	0.7%	1	0.2%
	CONSTIPATION	0	.	3	0.7%	3	0.7%	0	.
	DIARRHEA	1	0.2%	3	0.7%	4	1.0%	1	0.2%
	DYSPEPSIA	1	0.2%	2	0.5%	4	1.0%	0	.
	GASTRITIS	0	.	1	0.2%	0	.	1	0.2%
	GASTROENTERITIS	0	.	2	0.5%	1	0.2%	1	0.2%
	NAUSEA	0	.	3	0.7%	4	1.0%	2	0.5%
	PERIODONTITIS	0	.	2	0.5%	3	0.7%	0	.
	VOMITING	0	.	1	0.2%	8	1.9%	2	0.5%
HEART RATE AND RHYTHM	TOTAL	2	0.5%	1	0.2%	3	0.7%	1	0.2%
	EXTRASYSTOLES	2	0.5%	0	.	3	0.7%	1	0.2%
	TACHYCARDIA	0	.	1	0.2%	0	.	0	.

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INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		421-504		505-588		589-672		673-756	
		(N= 377)		(N= 362)		(N= 342)		(N= 330)	
		n	(%)	n	(%)	n	(%)	n	(%)
TOTAL PATIENTS WITH ADVERSE EXPERIENCES	TOTAL	109	28.9%	93	25.7%	76	22.2%	70	21.2%
BODY AS A WHOLE GENERAL	TOTAL	8	2.1%	6	1.7%	10	2.9%	7	2.1%
	ASTHENIA	2	0.5%	2	0.6%	1	0.3%	0	.
	CHEST PAIN	4	1.1%	0	.	1	0.3%	2	0.6%
	FATIGUE	0	.	0	.	0	.	0	.
	FEVER	1	0.3%	0	.	0	.	0	.
	INJURY	2	0.5%	2	0.6%	6	1.8%	3	0.9%
	MALAISE	1	0.3%	0	.	0	.	0	.
	PAIN	0	.	2	0.6%	2	0.6%	2	0.6%
CARDIOVASCULAR GENERAL	TOTAL	3	0.8%	2	0.6%	1	0.3%	3	0.9%
	HYPERTENSION	3	0.8%	2	0.6%	1	0.3%	3	0.9%
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	TOTAL	1	0.3%	10	2.8%	3	0.9%	5	1.5%
	DIZZINESS	0	.	3	0.8%	1	0.3%	1	0.3%
	HEADACHE	0	.	4	1.1%	2	0.6%	3	0.9%
	NEURALGIA	0	.	1	0.3%	0	.	1	0.3%
	VERTIGO	1	0.3%	4	1.1%	0	.	1	0.3%
GASTROINTESTINAL SYSTEM	TOTAL	8	2.1%	10	2.8%	7	2.0%	9	2.7%
	ABDOMINAL PAIN	3	0.8%	3	0.8%	2	0.6%	3	0.9%
	CONSTIPATION	0	.	1	0.3%	1	0.3%	1	0.3%
	DIARRHEA	2	0.5%	1	0.3%	1	0.3%	1	0.3%
	DYSPEPSIA	1	0.3%	1	0.3%	0	.	3	0.9%
	GASTRITIS	2	0.5%	0	.	1	0.3%	0	.
	GASTROENTERITIS	0	.	2	0.6%	1	0.3%	0	.
	NAUSEA	1	0.3%	2	0.6%	2	0.6%	1	0.3%
	PERIODONTITIS	0	.	0	.	0	.	0	.
	VOMITING	0	.	1	0.3%	0	.	1	0.3%
HEART RATE AND RHYTHM	TOTAL	2	0.5%	1	0.3%	0	.	1	0.3%
	EXTRASYSTOLES	0	.	0	.	0	.	0	.
	TACHYCARDIA	2	0.5%	1	0.3%	0	.	1	0.3%

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INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		757-840		841-924		925-1008		1009-1092	
		(N= 270)		(N= 182)		(N= 48)		(N= 0)	
		n	(%)	n	(%)	n	(%)	n	(%)
TOTAL PATIENTS WITH ADVERSE EXPERIENCES	TOTAL	34	12.6%	25	13.7%	4	8.3%	0	.
BODY AS A WHOLE GENERAL	TOTAL	7	2.6%	1	0.5%	0	.	0	.
	ASTHENIA	0	.	0	.	0	.	0	.
	CHEST PAIN	2	0.7%	0	.	0	.	0	.
	FATIGUE	1	0.4%	0	.	0	.	0	.
	FEVER	0	.	0	.	0	.	0	.
	INJURY	4	1.5%	1	0.5%	0	.	0	.
	MALAISE	0	.	0	.	0	.	0	.
	PAIN	0	.	0	.	0	.	0	.
CARDIOVASCULAR GENERAL	TOTAL	1	0.4%	0	.	0	.	0	.
	HYPERTENSION	1	0.4%	0	.	0	.	0	.
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	TOTAL	0	.	0	.	0	.	0	.
	DIZZINESS	0	.	0	.	0	.	0	.
	HEADACHE	0	.	0	.	0	.	0	.
	NEURALGIA	0	.	0	.	0	.	0	.
	VERTIGO	0	.	0	.	0	.	0	.
GASTROINTESTINAL SYSTEM	TOTAL	5	1.9%	6	3.3%	0	.	0	.
	ABDOMINAL PAIN	1	0.4%	1	0.5%	0	.	0	.
	CONSTIPATION	2	0.7%	1	0.5%	0	.	0	.
	DIARRHEA	0	.	1	0.5%	0	.	0	.
	DYSPEPSIA	0	.	0	.	0	.	0	.
	GASTRITIS	2	0.7%	0	.	0	.	0	.
	GASTROENTERITIS	0	.	1	0.5%	0	.	0	.
	NAUSEA	1	0.4%	0	.	0	.	0	.
	PERIODONTITIS	0	.	2	1.1%	0	.	0	.
	VOMITING	1	0.4%	0	.	0	.	0	.
HEART RATE AND RHYTHM	TOTAL	1	0.4%	1	0.5%	0	.	0	.
	EXTRASYSTOLES	0	.	0	.	0	.	0	.
	TACHYCARDIA	1	0.4%	1	0.5%	0	.	0	.

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SB 207499

TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND
PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE			
		1093-1176 (N= 0)		TOTAL (N= 480)	
		n	(%)	n	(%)
TOTAL PATIENTS WITH ADVERSE EXPERIENCES	TOTAL	0	.	446	92.9%
BODY AS A WHOLE GENERAL	TOTAL	0	.	120	25.0%
	ASTHENIA	0	.	15	3.1%
	CHEST PAIN	0	.	26	5.4%
	FATIGUE	0	.	9	1.9%
	FEVER	0	.	8	1.7%
	INJURY	0	.	62	12.9%
	MALAISE	0	.	6	1.3%
	PAIN	0	.	22	4.6%
CARDIOVASCULAR GENERAL	TOTAL	0	.	32	6.7%
	HYPERTENSION	0	.	32	6.7%
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	TOTAL	0	.	81	16.9%
	DIZZINESS	0	.	25	5.2%
	HEADACHE	0	.	47	9.8%
	NEURALGIA	0	.	11	2.3%
	VERTIGO	0	.	13	2.7%
GASTROINTESTINAL SYSTEM	TOTAL	0	.	179	37.3%
	ABDOMINAL PAIN	0	.	63	13.1%
	CONSTIPATION	0	.	15	3.1%
	DIARRHEA	0	.	51	10.6%
	DYSPEPSIA	0	.	35	7.3%
	GASTRITIS	0	.	12	2.5%
	GASTROENTERITIS	0	.	13	2.7%
	NAUSEA	0	.	38	7.9%
	PERIODONTITIS	0	.	12	2.5%
	VOMITING	0	.	20	4.2%
HEART RATE AND RHYTHM	TOTAL	0	.	24	5.0%
	EXTRASYSTOLES	0	.	13	2.7%
	TACHYCARDIA	0	.	11	2.3%

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4. EVENTS FOR WHICH THE ONSET IS UNDETERMINED ARE ASSUMED TO HAVE OCCURRED AT DAY 1

TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		1		2-7		8-14		15-28	
		(N= 480)		(N= 479)		(N= 468)		(N= 465)	
		n	(%)	n	(%)	n	(%)	n	(%)
LIVER AND BILIARY SYSTEM	TOTAL	0	.	0	.	2	0.4%	0	.
	GAMMA-GT INCREASED	0	.	0	.	1	0.2%	0	.
	HEPATIC ENZYMES INCREASED	0	.	0	.	1	0.2%	0	.
METABOLIC AND NUTRITIONAL	TOTAL	0	.	0	.	1	0.2%	5	1.1%
	HYPERGLYCEMIA	0	.	0	.	1	0.2%	5	1.1%
	WEIGHT DECREASE	0	.	0	.	0	.	0	.
MUSCULOSKELETAL SYSTEM	TOTAL	1	0.2%	4	0.8%	2	0.4%	8	1.7%
	ARTHRALGIA	0	.	1	0.2%	0	.	1	0.2%
	ARTHRITIS	0	.	0	.	0	.	1	0.2%
	BACK PAIN	1	0.2%	3	0.6%	2	0.4%	6	1.3%
	MYALGIA	0	.	0	.	0	.	0	.
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	TOTAL	0	.	0	.	0	.	0	.
	ANGINA PECTORIS	0	.	0	.	0	.	0	.
NEOPLASM	TOTAL	0	.	0	.	0	.	0	.
	NEOPLASM NOS	0	.	0	.	0	.	0	.
PSYCHIATRIC	TOTAL	0	.	2	0.4%	2	0.4%	2	0.4%
	ANXIETY	0	.	0	.	1	0.2%	1	0.2%
	DEPRESSION	0	.	0	.	0	.	0	.
	INSOMNIA	0	.	2	0.4%	1	0.2%	2	0.4%
REPRODUCTIVE MALE	TOTAL	0	.	0	.	0	.	0	.
	PROSTATIC DISORDER	0	.	0	.	0	.	0	.
RESISTANCE MECHANISM	TOTAL	0	.	0	.	2	0.4%	3	0.6%
	INFECTION	0	.	0	.	0	.	1	0.2%
	INFECTION VIRAL	0	.	0	.	1	0.2%	2	0.4%
	UPPER RESP TRACT INFECTION	0	.	0	.	1	0.2%	0	.
RESPIRATORY SYSTEM	TOTAL	3	0.6%	33	6.9%	26	5.6%	32	6.9%
	BRONCHITIS	0	.	0	.	0	.	1	0.2%

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TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		29-56 (N= 459)		57-84 (N= 451)		85-112 (N= 444)		113-140 (N= 438)	
		n	(%)	n	(%)	n	(%)	n	(%)
LIVER AND BILIARY SYSTEM	TOTAL	1	0.2%	0	.	2	0.5%	0	.
	GAMMA-GT INCREASED	0	.	0	.	0	.	0	.
	HEPATIC ENZYMES INCREASED	1	0.2%	0	.	2	0.5%	0	.
METABOLIC AND NUTRITIONAL	TOTAL	1	0.2%	1	0.2%	0	.	2	0.5%
	HYPERGLYCEMIA	1	0.2%	1	0.2%	0	.	1	0.2%
	WEIGHT DECREASE	0	.	0	.	0	.	1	0.2%
MUSCULOSKELETAL SYSTEM	TOTAL	8	1.7%	13	2.9%	4	0.9%	6	1.4%
	ARTHRALGIA	3	0.7%	2	0.4%	0	.	3	0.7%
	ARTHRITIS	0	.	3	0.7%	1	0.2%	0	.
	BACK PAIN	4	0.9%	6	1.3%	2	0.5%	1	0.2%
	MYALGIA	1	0.2%	2	0.4%	1	0.2%	2	0.5%
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	TOTAL	1	0.2%	0	.	0	.	0	.
	ANGINA PECTORIS	1	0.2%	0	.	0	.	0	.
NEOPLASM	TOTAL	0	.	0	.	0	.	0	.
	NEOPLASM NOS	0	.	0	.	0	.	0	.
PSYCHIATRIC	TOTAL	3	0.7%	1	0.2%	2	0.5%	6	1.4%
	ANXIETY	0	.	0	.	0	.	2	0.5%
	DEPRESSION	3	0.7%	0	.	1	0.2%	2	0.5%
	INSOMNIA	0	.	1	0.2%	1	0.2%	2	0.5%
REPRODUCTIVE MALE	TOTAL	0	.	1	0.2%	0	.	1	0.2%
	PROSTATIC DISORDER	0	.	1	0.2%	0	.	1	0.2%
RESISTANCE MECHANISM	TOTAL	8	1.7%	8	1.8%	10	2.3%	10	2.3%
	INFECTION	1	0.2%	0	.	0	.	0	.
	INFECTION VIRAL	4	0.9%	4	0.9%	4	0.9%	5	1.1%
	UPPER RESP TRACT INFECTION	3	0.7%	5	1.1%	6	1.4%	5	1.1%
RESPIRATORY SYSTEM	TOTAL	50	10.9%	40	8.9%	35	7.9%	31	7.1%
	BRONCHITIS	1	0.2%	0	.	0	.	0	.

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INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		141-168		169-252		253-336		337-420	
		(N= 435)		(N= 431)		(N= 413)		(N= 402)	
		n	(%)	n	(%)	n	(%)	n	(%)
LIVER AND BILIARY SYSTEM	TOTAL	1	0.2%	3	0.7%	5	1.2%	0	.
	GAMMA-GT INCREASED	1	0.2%	1	0.2%	3	0.7%	0	.
	HEPATIC ENZYMES INCREASED	0	.	2	0.5%	2	0.5%	0	.
METABOLIC AND NUTRITIONAL	TOTAL	3	0.7%	6	1.4%	4	1.0%	2	0.5%
	HYPERGLYCEMIA	1	0.2%	4	0.9%	3	0.7%	1	0.2%
	WEIGHT DECREASE	2	0.5%	2	0.5%	1	0.2%	1	0.2%
MUSCULOSKELETAL SYSTEM	TOTAL	6	1.4%	8	1.9%	6	1.5%	12	3.0%
	ARTHRALGIA	3	0.7%	1	0.2%	2	0.5%	2	0.5%
	ARTHRITIS	0	.	1	0.2%	0	.	1	0.2%
	BACK PAIN	2	0.5%	5	1.2%	4	1.0%	8	2.0%
	MYALGIA	1	0.2%	1	0.2%	1	0.2%	1	0.2%
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	TOTAL	1	0.2%	0	.	1	0.2%	2	0.5%
	ANGINA PECTORIS	1	0.2%	0	.	1	0.2%	2	0.5%
NEOPLASM	TOTAL	0	.	4	0.9%	1	0.2%	1	0.2%
	NEOPLASM NOS	0	.	4	0.9%	1	0.2%	1	0.2%
PSYCHIATRIC	TOTAL	1	0.2%	5	1.2%	9	2.2%	2	0.5%
	ANXIETY	0	.	0	.	2	0.5%	0	.
	DEPRESSION	1	0.2%	0	.	6	1.5%	2	0.5%
	INSOMNIA	0	.	5	1.2%	2	0.5%	0	.
REPRODUCTIVE MALE	TOTAL	0	.	1	0.2%	0	.	0	.
	PROSTATIC DISORDER	0	.	1	0.2%	0	.	0	.
RESISTANCE MECHANISM	TOTAL	3	0.7%	9	2.1%	8	1.9%	8	2.0%
	INFECTION	1	0.2%	0	.	2	0.5%	2	0.5%
	INFECTION VIRAL	2	0.5%	3	0.7%	4	1.0%	2	0.5%
	UPPER RESP TRACT INFECTION	0	.	6	1.4%	3	0.7%	4	1.0%
RESPIRATORY SYSTEM	TOTAL	34	7.8%	45	10.4%	41	9.9%	39	9.7%
	BRONCHITIS	1	0.2%	0	.	4	1.0%	1	0.2%

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INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		421-504 (N= 377)		505-588 (N= 362)		589-672 (N= 342)		673-756 (N= 330)	
		n	(%)	n	(%)	n	(%)	n	(%)
LIVER AND BILIARY SYSTEM	TOTAL	2	0.5%	1	0.3%	2	0.6%	1	0.3%
	GAMMA-GT INCREASED	1	0.3%	0	.	1	0.3%	0	.
	HEPATIC ENZYMES INCREASED	1	0.3%	1	0.3%	1	0.3%	1	0.3%
METABOLIC AND NUTRITIONAL	TOTAL	2	0.5%	1	0.3%	2	0.6%	3	0.9%
	HYPERGLYCEMIA	1	0.3%	1	0.3%	1	0.3%	2	0.6%
	WEIGHT DECREASE	1	0.3%	0	.	1	0.3%	1	0.3%
MUSCULOSKELETAL SYSTEM	TOTAL	9	2.4%	8	2.2%	6	1.8%	6	1.8%
	ARTHRALGIA	3	0.8%	3	0.8%	2	0.6%	2	0.6%
	ARTHRITIS	1	0.3%	0	.	4	1.2%	0	.
	BACK PAIN	5	1.3%	3	0.8%	0	.	3	0.9%
	MYALGIA	0	.	2	0.6%	0	.	1	0.3%
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	TOTAL	4	1.1%	2	0.6%	0	.	0	.
	ANGINA PECTORIS	4	1.1%	2	0.6%	0	.	0	.
NEOPLASM	TOTAL	0	.	1	0.3%	0	.	1	0.3%
	NEOPLASM NOS	0	.	1	0.3%	0	.	1	0.3%
PSYCHIATRIC	TOTAL	3	0.8%	4	1.1%	2	0.6%	4	1.2%
	ANXIETY	1	0.3%	3	0.8%	1	0.3%	0	.
	DEPRESSION	0	.	1	0.3%	1	0.3%	2	0.6%
	INSOMNIA	2	0.5%	0	.	1	0.3%	2	0.6%
REPRODUCTIVE MALE	TOTAL	0	.	2	0.6%	0	.	1	0.3%
	PROSTATIC DISORDER	0	.	2	0.6%	0	.	1	0.3%
RESISTANCE MECHANISM	TOTAL	9	2.4%	6	1.7%	6	1.8%	4	1.2%
	INFECTION	3	0.8%	1	0.3%	0	.	0	.
	INFECTION VIRAL	1	0.3%	1	0.3%	2	0.6%	2	0.6%
	UPPER RESP TRACT INFECTION	5	1.3%	4	1.1%	4	1.2%	2	0.6%
RESPIRATORY SYSTEM	TOTAL	41	10.9%	25	6.9%	9	2.6%	14	4.2%
	BRONCHITIS	1	0.3%	1	0.3%	3	0.9%	0	.

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TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		757-840		841-924		925-1008		1009-1092	
		(N= 270)		(N= 182)		(N= 48)		(N= 0)	
		n	(%)	n	(%)	n	(%)	n	(%)
LIVER AND BILIARY SYSTEM	TOTAL	1	0.4%	0	.	0	.	0	.
	GAMMA-GT INCREASED	1	0.4%	0	.	0	.	0	.
	HEPATIC ENZYMES INCREASED	0	.	0	.	0	.	0	.
METABOLIC AND NUTRITIONAL	TOTAL	1	0.4%	0	.	0	.	0	.
	HYPERGLYCEMIA	0	.	0	.	0	.	0	.
	WEIGHT DECREASE	1	0.4%	0	.	0	.	0	.
MUSCULOSKELETAL SYSTEM	TOTAL	2	0.7%	1	0.5%	0	.	0	.
	ARTHRALGIA	2	0.7%	0	.	0	.	0	.
	ARTHRITIS	0	.	0	.	0	.	0	.
	BACK PAIN	0	.	1	0.5%	0	.	0	.
	MYALGIA	0	.	0	.	0	.	0	.
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	TOTAL	0	.	0	.	0	.	0	.
	ANGINA PECTORIS	0	.	0	.	0	.	0	.
NEOPLASM	TOTAL	0	.	1	0.5%	0	.	0	.
	NEOPLASM NOS	0	.	1	0.5%	0	.	0	.
PSYCHIATRIC	TOTAL	4	1.5%	1	0.5%	0	.	0	.
	ANXIETY	1	0.4%	0	.	0	.	0	.
	DEPRESSION	1	0.4%	1	0.5%	0	.	0	.
	INSOMNIA	2	0.7%	0	.	0	.	0	.
REPRODUCTIVE MALE	TOTAL	0	.	0	.	0	.	0	.
	PROSTATIC DISORDER	0	.	0	.	0	.	0	.
RESISTANCE MECHANISM	TOTAL	4	1.5%	1	0.5%	0	.	0	.
	INFECTION	0	.	0	.	0	.	0	.
	INFECTION VIRAL	2	0.7%	0	.	0	.	0	.
	UPPER RESP TRACT INFECTION	2	0.7%	1	0.5%	0	.	0	.
RESPIRATORY SYSTEM	TOTAL	7	2.6%	5	2.7%	0	.	0	.
	BRONCHITIS	1	0.4%	0	.	0	.	0	.

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SB 207499

TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE			
		1093-1176 (N= 0)		TOTAL (N= 480)	
		n	(%)	n	(%)
LIVER AND BILIARY SYSTEM	TOTAL	0	.	21	4.4%
	GAMMA-GT INCREASED	0	.	9	1.9%
	HEPATIC ENZYMES INCREASED	0	.	12	2.5%
METABOLIC AND NUTRITIONAL	TOTAL	0	.	34	7.1%
	HYPERGLYCEMIA	0	.	23	4.8%
	WEIGHT DECREASE	0	.	11	2.3%
MUSCULOSKELETAL SYSTEM	TOTAL	0	.	95	19.8%
	ARTHRALGIA	0	.	30	6.3%
	ARTHRITIS	0	.	12	2.5%
	BACK PAIN	0	.	56	11.7%
	MYALGIA	0	.	13	2.7%
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	TOTAL	0	.	11	2.3%
	ANGINA PECTORIS	0	.	11	2.3%
NEOPLASM	TOTAL	0	.	9	1.9%
	NEOPLASM NOS	0	.	9	1.9%
PSYCHIATRIC	TOTAL	0	.	47	9.8%
	ANXIETY	0	.	12	2.5%
	DEPRESSION	0	.	21	4.4%
	INSOMNIA	0	.	23	4.8%
REPRODUCTIVE MALE	TOTAL	0	.	6	1.3%
	PROSTATIC DISORDER	0	.	6	1.3%
RESISTANCE MECHANISM	TOTAL	0	.	91	19.0%
	INFECTION	0	.	11	2.3%
	INFECTION VIRAL	0	.	39	8.1%
	UPPER RESP TRACT INFECTION	0	.	51	10.6%
RESPIRATORY SYSTEM	TOTAL	0	.	354	73.8%
	BRONCHITIS	0	.	14	2.9%

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PROTOCOL 040

PRIOR TREATMENT: SB 207499

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		1		2-7		8-14		15-28	
		(N= 480)		(N= 479)		(N= 468)		(N= 465)	
		n	(%)	n	(%)	n	(%)	n	(%)
RESPIRATORY SYSTEM	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	1	0.2%	25	5.2%	23	4.9%	28	6.0%
	COUGHING	1	0.2%	1	0.2%	1	0.2%	0	.
	DYSPNEA	0	.	0	.	1	0.2%	0	.
	PHARYNGITIS	1	0.2%	1	0.2%	0	.	3	0.6%
	PNEUMONIA	0	.	0	.	0	.	0	.
	RESPIRATORY DISORDER	0	.	1	0.2%	0	.	2	0.4%
	RHINITIS	1	0.2%	4	0.8%	1	0.2%	1	0.2%
	SINUSITIS	0	.	1	0.2%	0	.	0	.
SKIN AND APPENDAGES	TOTAL	0	.	0	.	1	0.2%	0	.
	PRURITUS	0	.	0	.	1	0.2%	0	.
URINARY SYSTEM	TOTAL	2	0.4%	0	.	1	0.2%	3	0.6%
	ALBUMINURIA	0	.	0	.	1	0.2%	0	.
	HEMATURIA	0	.	0	.	0	.	2	0.4%
	PYURIA	1	0.2%	0	.	0	.	0	.
	URINARY TRACT INFECTION	1	0.2%	0	.	0	.	1	0.2%
VISION	TOTAL	0	.	0	.	0	.	1	0.2%
	CONJUNCTIVITIS	0	.	0	.	0	.	1	0.2%
WHITE CELL AND RETICULOENDOTHELIAL SYSTE	TOTAL	0	.	1	0.2%	1	0.2%	1	0.2%
	LEUKOCYTOSIS	0	.	1	0.2%	1	0.2%	1	0.2%

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4. EVENTS FOR WHICH THE ONSET IS UNDETERMINED ARE ASSUMED TO HAVE OCCURRED AT DAY 1

TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		29-56 (N= 459)		57-84 (N= 451)		85-112 (N= 444)		113-140 (N= 438)	
		n	(%)	n	(%)	n	(%)	n	(%)
RESPIRATORY SYSTEM	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	35	7.6%	30	6.7%	23	5.2%	25	5.7%
	COUGHING	3	0.7%	2	0.4%	3	0.7%	2	0.5%
	DYSPNEA	0	.	0	.	0	.	0	.
	PHARYNGITIS	6	1.3%	2	0.4%	4	0.9%	3	0.7%
	PNEUMONIA	1	0.2%	2	0.4%	1	0.2%	1	0.2%
	RESPIRATORY DISORDER	1	0.2%	1	0.2%	3	0.7%	0	.
	RHINITIS	3	0.7%	3	0.7%	1	0.2%	1	0.2%
	SINUSITIS	2	0.4%	1	0.2%	2	0.5%	0	.
SKIN AND APPENDAGES	TOTAL	1	0.2%	3	0.7%	1	0.2%	0	.
	PRURITUS	1	0.2%	3	0.7%	1	0.2%	0	.
URINARY SYSTEM	TOTAL	4	0.9%	6	1.3%	2	0.5%	4	0.9%
	ALBUMINURIA	0	.	0	.	0	.	2	0.5%
	HEMATURIA	1	0.2%	1	0.2%	0	.	1	0.2%
	PYURIA	0	.	2	0.4%	1	0.2%	1	0.2%
	URINARY TRACT INFECTION	3	0.7%	3	0.7%	2	0.5%	0	.
VISION	TOTAL	1	0.2%	0	.	0	.	1	0.2%
	CONJUNCTIVITIS	1	0.2%	0	.	0	.	1	0.2%
WHITE CELL AND RETICULOENDOTHELIAL SYSTE	TOTAL	2	0.4%	0	.	1	0.2%	1	0.2%
	LEUKOCYTOSIS	2	0.4%	0	.	1	0.2%	1	0.2%

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM AND PREFERRED TERM
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS AT EACH TIME INTERVAL
3. ONLY EVENTS OCCURING IN AT LEAST 2% OF PATIENTS ENROLLED TO SB 207499 ARE INCLUDED
4. EVENTS FOR WHICH THE ONSET IS UNDETERMINED ARE ASSUMED TO HAVE OCCURRED AT DAY 1

TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND
PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		141-168		169-252		253-336		337-420	
		(N= 435)		(N= 431)		(N= 413)		(N= 402)	
		n	(%)	n	(%)	n	(%)	n	(%)
RESPIRATORY SYSTEM	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	21	4.8%	35	8.1%	16	3.9%	22	5.5%
	COUGHING	3	0.7%	0	.	3	0.7%	4	1.0%
	DYSPNEA	2	0.5%	1	0.2%	2	0.5%	0	.
	PHARYNGITIS	2	0.5%	1	0.2%	7	1.7%	4	1.0%
	PNEUMONIA	2	0.5%	1	0.2%	0	.	1	0.2%
	RESPIRATORY DISORDER	2	0.5%	2	0.5%	7	1.7%	3	0.7%
	RHINITIS	3	0.7%	6	1.4%	4	1.0%	2	0.5%
	SINUSITIS	1	0.2%	1	0.2%	2	0.5%	2	0.5%
SKIN AND APPENDAGES	TOTAL	0	.	2	0.5%	2	0.5%	0	.
	PRURITUS	0	.	2	0.5%	2	0.5%	0	.
URINARY SYSTEM	TOTAL	3	0.7%	6	1.4%	8	1.9%	11	2.7%
	ALBUMINURIA	1	0.2%	1	0.2%	2	0.5%	3	0.7%
	HEMATURIA	0	.	2	0.5%	4	1.0%	2	0.5%
	PYURIA	2	0.5%	0	.	0	.	2	0.5%
	URINARY TRACT INFECTION	0	.	3	0.7%	2	0.5%	6	1.5%
VISION	TOTAL	0	.	1	0.2%	1	0.2%	0	.
	CONJUNCTIVITIS	0	.	1	0.2%	1	0.2%	0	.
WHITE CELL AND RETICULOENDOTHELIAL SYSTE	TOTAL	0	.	0	.	3	0.7%	3	0.7%
	LEUKOCYTOSIS	0	.	0	.	3	0.7%	3	0.7%

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM AND PREFERRED TERM
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3. ONLY EVENTS OCCURING IN AT LEAST 2% OF PATIENTS ENROLLED TO SB 207499 ARE INCLUDED
4. EVENTS FOR WHICH THE ONSET IS UNDETERMINED ARE ASSUMED TO HAVE OCCURRED AT DAY 1

TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		421-504 (N= 377)		505-588 (N= 362)		589-672 (N= 342)		673-756 (N= 330)	
		n	(%)	n	(%)	n	(%)	n	(%)
RESPIRATORY SYSTEM	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	20	5.3%	9	2.5%	1	0.3%	6	1.8%
	COUGHING	2	0.5%	1	0.3%	1	0.3%	2	0.6%
	DYSPNEA	2	0.5%	1	0.3%	0	.	2	0.6%
	PHARYNGITIS	2	0.5%	5	1.4%	1	0.3%	0	.
	PNEUMONIA	1	0.3%	3	0.8%	1	0.3%	0	.
	RESPIRATORY DISORDER	4	1.1%	0	.	0	.	2	0.6%
	RHINITIS	6	1.6%	4	1.1%	2	0.6%	2	0.6%
	SINUSITIS	3	0.8%	1	0.3%	0	.	0	.
SKIN AND APPENDAGES	TOTAL	1	0.3%	0	.	2	0.6%	1	0.3%
	PRURITUS	1	0.3%	0	.	2	0.6%	1	0.3%
URINARY SYSTEM	TOTAL	2	0.5%	1	0.3%	2	0.6%	0	.
	ALBUMINURIA	1	0.3%	0	.	0	.	0	.
	HEMATURIA	0	.	0	.	0	.	0	.
	PYURIA	1	0.3%	1	0.3%	1	0.3%	0	.
	URINARY TRACT INFECTION	0	.	0	.	1	0.3%	0	.
VISION	TOTAL	2	0.5%	0	.	1	0.3%	0	.
	CONJUNCTIVITIS	2	0.5%	0	.	1	0.3%	0	.
WHITE CELL AND RETICULOENDOTHELIAL SYSTE	TOTAL	0	.	0	.	2	0.6%	2	0.6%
	LEUKOCYTOSIS	0	.	0	.	2	0.6%	2	0.6%

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM AND PREFERRED TERM
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3. ONLY EVENTS OCCURING IN AT LEAST 2% OF PATIENTS ENROLLED TO SB 207499 ARE INCLUDED
4. EVENTS FOR WHICH THE ONSET IS UNDETERMINED ARE ASSUMED TO HAVE OCCURRED AT DAY 1

TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		757-840		841-924		925-1008		1009-1092	
		(N= 270)		(N= 182)		(N= 48)		(N= 0)	
		n	(%)	n	(%)	n	(%)	n	(%)
RESPIRATORY SYSTEM	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	4	1.5%	3	1.6%	0	.	0	.
	COUGHING	1	0.4%	1	0.5%	0	.	0	.
	DYSPNEA	1	0.4%	1	0.5%	0	.	0	.
	PHARYNGITIS	0	.	0	.	0	.	0	.
	PNEUMONIA	0	.	0	.	0	.	0	.
	RESPIRATORY DISORDER	0	.	0	.	0	.	0	.
	RHINITIS	0	.	0	.	0	.	0	.
	SINUSITIS	0	.	0	.	0	.	0	.
SKIN AND APPENDAGES	TOTAL	0	.	0	.	0	.	0	.
	PRURITUS	0	.	0	.	0	.	0	.
URINARY SYSTEM	TOTAL	0	.	1	0.5%	0	.	0	.
	ALBUMINURIA	0	.	1	0.5%	0	.	0	.
	HEMATURIA	0	.	0	.	0	.	0	.
	PYURIA	0	.	0	.	0	.	0	.
	URINARY TRACT INFECTION	0	.	0	.	0	.	0	.
VISION	TOTAL	0	.	0	.	0	.	0	.
	CONJUNCTIVITIS	0	.	0	.	0	.	0	.
WHITE CELL AND RETICULOENDOTHELIAL SYSTE	TOTAL	0	.	0	.	0	.	0	.
	LEUKOCYTOSIS	0	.	0	.	0	.	0	.

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM AND PREFERRED TERM
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3. ONLY EVENTS OCCURRING IN AT LEAST 2% OF PATIENTS ENROLLED TO SB 207499 ARE INCLUDED
4. EVENTS FOR WHICH THE ONSET IS UNDETERMINED ARE ASSUMED TO HAVE OCCURRED AT DAY 1

TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: SB 207499

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE			
		1093-1176 (N= 0)		TOTAL (N= 480)	
		n	(%)	n	(%)
RESPIRATORY SYSTEM	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	0	.	327	68.1%
	COUGHING	0	.	31	6.5%
	DYSPNEA	0	.	13	2.7%
	PHARYNGITIS	0	.	42	8.8%
	PNEUMONIA	0	.	14	2.9%
	RESPIRATORY DISORDER	0	.	28	5.8%
	RHINITIS	0	.	44	9.2%
	SINUSITIS	0	.	16	3.3%
SKIN AND APPENDAGES	TOTAL	0	.	14	2.9%
	PRURITUS	0	.	14	2.9%
URINARY SYSTEM	TOTAL	0	.	48	10.0%
	ALBUMINURIA	0	.	12	2.5%
	HEMATURIA	0	.	13	2.7%
	PYURIA	0	.	12	2.5%
	URINARY TRACT INFECTION	0	.	22	4.6%
VISION	TOTAL	0	.	8	1.7%
	CONJUNCTIVITIS	0	.	8	1.7%
WHITE CELL AND RETICULOENDOTHELIAL SYSTE	TOTAL	0	.	17	3.5%
	LEUKOCYTOSIS	0	.	17	3.5%

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4. EVENTS FOR WHICH THE ONSET IS UNDETERMINED ARE ASSUMED TO HAVE OCCURRED AT DAY 1

TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL

		DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		1 (N= 723)		2-7 (N= 721)		8-14 (N= 705)		15-28 (N= 692)	
WHO BODY SYSTEM	WHO PREFERRED TERM	n	(%)	n	(%)	n	(%)	n	(%)
TOTAL PATIENTS WITH ADVERSE EXPERIENCES	TOTAL	46	6.4%	166	23.0%	116	16.5%	143	20.7%
BODY AS A WHOLE GENERAL	TOTAL	2	0.3%	11	1.5%	7	1.0%	8	1.2%
	ASTHENIA	0	.	3	0.4%	1	0.1%	0	.
	CHEST PAIN	0	.	0	.	0	.	2	0.3%
	FATIGUE	0	.	4	0.6%	3	0.4%	0	.
	FEVER	0	.	1	0.1%	2	0.3%	1	0.1%
	INJURY	0	.	0	.	1	0.1%	2	0.3%
	MALAISE	2	0.3%	4	0.6%	0	.	0	.
	PAIN	0	.	1	0.1%	1	0.1%	3	0.4%
CARDIOVASCULAR GENERAL	TOTAL	0	.	0	.	1	0.1%	4	0.6%
	HYPERTENSION	0	.	0	.	1	0.1%	4	0.6%
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	TOTAL	6	0.8%	28	3.9%	13	1.8%	7	1.0%
	DIZZINESS	2	0.3%	5	0.7%	5	0.7%	1	0.1%
	HEADACHE	5	0.7%	24	3.3%	6	0.9%	5	0.7%
	NEURALGIA	0	.	0	.	2	0.3%	1	0.1%
	VERTIGO	0	.	0	.	0	.	0	.
GASTROINTESTINAL SYSTEM	TOTAL	23	3.2%	87	12.1%	29	4.1%	28	4.0%
	ABDOMINAL PAIN	7	1.0%	24	3.3%	11	1.6%	11	1.6%
	CONSTIPATION	1	0.1%	1	0.1%	0	.	1	0.1%
	DIARRHEA	4	0.6%	27	3.7%	11	1.6%	6	0.9%
	DYSPEPSIA	2	0.3%	18	2.5%	3	0.4%	6	0.9%
	GASTRITIS	2	0.3%	3	0.4%	0	.	0	.
	GASTROENTERITIS	0	.	4	0.6%	0	.	0	.
	NAUSEA	9	1.2%	18	2.5%	5	0.7%	8	1.2%
	PERIODONTITIS	0	.	1	0.1%	1	0.1%	1	0.1%
	VOMITING	1	0.1%	8	1.1%	2	0.3%	2	0.3%
HEART RATE AND RHYTHM	TOTAL	2	0.3%	1	0.1%	2	0.3%	0	.
	EXTRASYSTOLES	0	.	1	0.1%	0	.	0	.
	TACHYCARDIA	2	0.3%	0	.	2	0.3%	0	.

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM AND PREFERRED TERM

2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS AT EACH TIME INTERVAL

3. ONLY EVENTS OCCURRING IN AT LEAST 2% OF PATIENTS ENROLLED TO SB 207499 ARE INCLUDED

4. EVENTS FOR WHICH THE ONSET IS UNDETERMINED ARE ASSUMED TO HAVE OCCURRED AT DAY 1

TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		29-56 (N= 679)		57-84 (N= 664)		85-112 (N= 651)		113-140 (N= 638)	
		n	(%)	n	(%)	n	(%)	n	(%)
TOTAL PATIENTS WITH ADVERSE EXPERIENCES	TOTAL	167	24.6%	163	24.5%	140	21.5%	140	21.9%
BODY AS A WHOLE GENERAL	TOTAL	8	1.2%	16	2.4%	15	2.3%	11	1.7%
	ASTHENIA	3	0.4%	0	.	1	0.2%	3	0.5%
	CHEST PAIN	2	0.3%	5	0.8%	2	0.3%	1	0.2%
	FATIGUE	0	.	0	.	0	.	0	.
	FEVER	0	.	2	0.3%	3	0.5%	2	0.3%
	INJURY	2	0.3%	7	1.1%	5	0.8%	3	0.5%
	MALAISE	1	0.1%	1	0.2%	1	0.2%	1	0.2%
	PAIN	1	0.1%	1	0.2%	3	0.5%	2	0.3%
CARDIOVASCULAR GENERAL	TOTAL	1	0.1%	2	0.3%	2	0.3%	2	0.3%
	HYPERTENSION	1	0.1%	2	0.3%	2	0.3%	2	0.3%
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	TOTAL	12	1.8%	8	1.2%	2	0.3%	3	0.5%
	DIZZINESS	4	0.6%	0	.	1	0.2%	0	.
	HEADACHE	7	1.0%	5	0.8%	1	0.2%	1	0.2%
	NEURALGIA	1	0.1%	2	0.3%	0	.	1	0.2%
	VERTIGO	0	.	1	0.2%	0	.	1	0.2%
GASTROINTESTINAL SYSTEM	TOTAL	22	3.2%	24	3.6%	15	2.3%	20	3.1%
	ABDOMINAL PAIN	8	1.2%	8	1.2%	2	0.3%	7	1.1%
	CONSTIPATION	0	.	0	.	0	.	0	.
	DIARRHEA	9	1.3%	7	1.1%	5	0.8%	4	0.6%
	DYSPEPSIA	3	0.4%	4	0.6%	3	0.5%	4	0.6%
	GASTRITIS	1	0.1%	0	.	2	0.3%	1	0.2%
	GASTROENTERITIS	0	.	2	0.3%	0	.	3	0.5%
	NAUSEA	3	0.4%	3	0.5%	2	0.3%	2	0.3%
	PERIODONTITIS	1	0.1%	0	.	1	0.2%	0	.
	VOMITING	3	0.4%	0	.	2	0.3%	2	0.3%
HEART RATE AND RHYTHM	TOTAL	1	0.1%	4	0.6%	2	0.3%	4	0.6%
	EXTRASYSTOLES	0	.	3	0.5%	2	0.3%	2	0.3%
	TACHYCARDIA	1	0.1%	1	0.2%	0	.	2	0.3%

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM AND PREFERRED TERM
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TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		141-168		169-252		253-336		337-420	
		(N= 631)		(N= 625)		(N= 600)		(N= 586)	
		n	(%)	n	(%)	n	(%)	n	(%)
TOTAL PATIENTS WITH ADVERSE EXPERIENCES	TOTAL	127	20.1%	237	37.9%	205	34.2%	182	31.1%
BODY AS A WHOLE GENERAL	TOTAL	15	2.4%	19	3.0%	26	4.3%	25	4.3%
	ASTHENIA	0	.	1	0.2%	0	.	4	0.7%
	CHEST PAIN	2	0.3%	3	0.5%	8	1.3%	4	0.7%
	FATIGUE	1	0.2%	1	0.2%	4	0.7%	2	0.3%
	FEVER	1	0.2%	0	.	1	0.2%	1	0.2%
	INJURY	10	1.6%	9	1.4%	10	1.7%	12	2.0%
	MALAISE	0	.	1	0.2%	2	0.3%	2	0.3%
	PAIN	1	0.2%	5	0.8%	3	0.5%	2	0.3%
CARDIOVASCULAR GENERAL	TOTAL	1	0.2%	6	1.0%	6	1.0%	4	0.7%
	HYPERTENSION	1	0.2%	6	1.0%	6	1.0%	4	0.7%
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	TOTAL	2	0.3%	14	2.2%	17	2.8%	6	1.0%
	DIZZINESS	0	.	3	0.5%	3	0.5%	2	0.3%
	HEADACHE	2	0.3%	6	1.0%	6	1.0%	2	0.3%
	NEURALGIA	0	.	2	0.3%	5	0.8%	2	0.3%
	VERTIGO	0	.	3	0.5%	3	0.5%	1	0.2%
GASTROINTESTINAL SYSTEM	TOTAL	9	1.4%	28	4.5%	33	5.5%	11	1.9%
	ABDOMINAL PAIN	3	0.5%	6	1.0%	6	1.0%	3	0.5%
	CONSTIPATION	0	.	4	0.6%	3	0.5%	0	.
	DIARRHEA	2	0.3%	6	1.0%	4	0.7%	1	0.2%
	DYSPEPSIA	1	0.2%	5	0.8%	5	0.8%	2	0.3%
	GASTRITIS	0	.	1	0.2%	0	.	1	0.2%
	GASTROENTERITIS	0	.	2	0.3%	1	0.2%	1	0.2%
	NAUSEA	2	0.3%	3	0.5%	6	1.0%	2	0.3%
	PERIODONTITIS	1	0.2%	3	0.5%	4	0.7%	0	.
	VOMITING	0	.	1	0.2%	9	1.5%	2	0.3%
HEART RATE AND RHYTHM	TOTAL	3	0.5%	1	0.2%	5	0.8%	4	0.7%
	EXTRASYSTOLES	3	0.5%	0	.	4	0.7%	2	0.3%
	TACHYCARDIA	0	.	1	0.2%	1	0.2%	2	0.3%

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM AND PREFERRED TERM
2. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS AT EACH TIME INTERVAL
3. ONLY EVENTS OCCURRING IN AT LEAST 2% OF PATIENTS ENROLLED TO SB 207499 ARE INCLUDED
4. EVENTS FOR WHICH THE ONSET IS UNDETERMINED ARE ASSUMED TO HAVE OCCURRED AT DAY 1

TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		421-504 (N= 551)		505-588 (N= 533)		589-672 (N= 505)		673-756 (N= 489)	
		n	(%)	n	(%)	n	(%)	n	(%)
TOTAL PATIENTS WITH ADVERSE EXPERIENCES	TOTAL	170	30.9%	133	25.0%	121	24.0%	99	20.2%
BODY AS A WHOLE GENERAL	TOTAL	15	2.7%	10	1.9%	14	2.8%	10	2.0%
	ASTHENIA	3	0.5%	2	0.4%	2	0.4%	0	.
	CHEST PAIN	6	1.1%	0	.	1	0.2%	3	0.6%
	FATIGUE	1	0.2%	0	.	0	.	0	.
	FEVER	2	0.4%	1	0.2%	1	0.2%	0	.
	INJURY	4	0.7%	5	0.9%	7	1.4%	4	0.8%
	MALAISE	1	0.2%	0	.	0	.	0	.
	PAIN	0	.	2	0.4%	3	0.6%	3	0.6%
CARDIOVASCULAR GENERAL	TOTAL	4	0.7%	2	0.4%	2	0.4%	4	0.8%
	HYPERTENSION	4	0.7%	2	0.4%	2	0.4%	4	0.8%
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	TOTAL	4	0.7%	10	1.9%	4	0.8%	5	1.0%
	DIZZINESS	3	0.5%	3	0.6%	1	0.2%	1	0.2%
	HEADACHE	0	.	4	0.8%	2	0.4%	3	0.6%
	NEURALGIA	0	.	1	0.2%	0	.	1	0.2%
	VERTIGO	1	0.2%	4	0.8%	1	0.2%	1	0.2%
GASTROINTESTINAL SYSTEM	TOTAL	19	3.4%	15	2.8%	13	2.6%	9	1.8%
	ABDOMINAL PAIN	4	0.7%	4	0.8%	3	0.6%	3	0.6%
	CONSTIPATION	2	0.4%	1	0.2%	2	0.4%	1	0.2%
	DIARRHEA	5	0.9%	1	0.2%	1	0.2%	1	0.2%
	DYSPEPSIA	3	0.5%	2	0.4%	1	0.2%	3	0.6%
	GASTRITIS	3	0.5%	1	0.2%	1	0.2%	0	.
	GASTROENTERITIS	2	0.4%	3	0.6%	3	0.6%	0	.
	NAUSEA	1	0.2%	2	0.4%	3	0.6%	1	0.2%
	PERIODONTITIS	1	0.2%	1	0.2%	0	.	0	.
	VOMITING	0	.	1	0.2%	0	.	1	0.2%
HEART RATE AND RHYTHM	TOTAL	3	0.5%	1	0.2%	1	0.2%	1	0.2%
	EXTRASYSTOLES	0	.	0	.	0	.	0	.
	TACHYCARDIA	3	0.5%	1	0.2%	1	0.2%	1	0.2%

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM AND PREFERRED TERM
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4. EVENTS FOR WHICH THE ONSET IS UNDETERMINED ARE ASSUMED TO HAVE OCCURRED AT DAY 1

TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		757-840 (N= 399)		841-924 (N= 263)		925-1008 (N= 77)		1009-1092 (N= 0)	
		n	(%)	n	(%)	n	(%)	n	(%)
TOTAL PATIENTS WITH ADVERSE EXPERIENCES	TOTAL	58	14.5%	37	14.1%	5	6.5%	0	.
BODY AS A WHOLE GENERAL	TOTAL	10	2.5%	1	0.4%	0	.	0	.
	ASTHENIA	0	.	0	.	0	.	0	.
	CHEST PAIN	2	0.5%	0	.	0	.	0	.
	FATIGUE	1	0.3%	0	.	0	.	0	.
	FEVER	1	0.3%	0	.	0	.	0	.
	INJURY	6	1.5%	1	0.4%	0	.	0	.
	MALAISE	0	.	0	.	0	.	0	.
	PAIN	0	.	0	.	0	.	0	.
CARDIOVASCULAR GENERAL	TOTAL	1	0.3%	0	.	0	.	0	.
	HYPERTENSION	1	0.3%	0	.	0	.	0	.
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	TOTAL	1	0.3%	0	.	1	1.3%	0	.
	DIZZINESS	0	.	0	.	0	.	0	.
	HEADACHE	0	.	0	.	0	.	0	.
	NEURALGIA	0	.	0	.	0	.	0	.
	VERTIGO	1	0.3%	0	.	1	1.3%	0	.
GASTROINTESTINAL SYSTEM	TOTAL	9	2.3%	7	2.7%	0	.	0	.
	ABDOMINAL PAIN	2	0.5%	1	0.4%	0	.	0	.
	CONSTIPATION	3	0.8%	1	0.4%	0	.	0	.
	DIARRHEA	0	.	1	0.4%	0	.	0	.
	DYSPEPSIA	0	.	0	.	0	.	0	.
	GASTRITIS	2	0.5%	0	.	0	.	0	.
	GASTROENTERITIS	1	0.3%	2	0.8%	0	.	0	.
	NAUSEA	2	0.5%	0	.	0	.	0	.
	PERIODONTITIS	0	.	2	0.8%	0	.	0	.
	VOMITING	1	0.3%	0	.	0	.	0	.
HEART RATE AND RHYTHM	TOTAL	1	0.3%	2	0.8%	0	.	0	.
	EXTRASYSTOLES	0	.	0	.	0	.	0	.
	TACHYCARDIA	1	0.3%	2	0.8%	0	.	0	.

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TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE			
		1093-1176 (N= 0)		TOTAL (N= 723)	
		n	(%)	n	(%)
TOTAL PATIENTS WITH ADVERSE EXPERIENCES	TOTAL	0	.	675	93.4%
BODY AS A WHOLE GENERAL	TOTAL	0	.	185	25.6%
	ASTHENIA	0	.	23	3.2%
	CHEST PAIN	0	.	41	5.7%
	FATIGUE	0	.	17	2.4%
	FEVER	0	.	19	2.6%
	INJURY	0	.	88	12.2%
	MALAISE	0	.	16	2.2%
	PAIN	0	.	31	4.3%
CARDIOVASCULAR GENERAL	TOTAL	0	.	42	5.8%
	HYPERTENSION	0	.	42	5.8%
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	TOTAL	0	.	129	17.8%
	DIZZINESS	0	.	34	4.7%
	HEADACHE	0	.	79	10.9%
	NEURALGIA	0	.	18	2.5%
	VERTIGO	0	.	18	2.5%
GASTROINTESTINAL SYSTEM	TOTAL	0	.	301	41.6%
	ABDOMINAL PAIN	0	.	113	15.6%
	CONSTIPATION	0	.	20	2.8%
	DIARRHEA	0	.	95	13.1%
	DYSPEPSIA	0	.	65	9.0%
	GASTRITIS	0	.	18	2.5%
	GASTROENTERITIS	0	.	24	3.3%
	NAUSEA	0	.	72	10.0%
	PERIODONTITIS	0	.	17	2.4%
	VOMITING	0	.	35	4.8%
HEART RATE AND RHYTHM	TOTAL	0	.	38	5.3%
	EXTRASYSTOLES	0	.	17	2.4%
	TACHYCARDIA	0	.	21	2.9%

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INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		1		2-7		8-14		15-28	
		(N= 723)		(N= 721)		(N= 705)		(N= 692)	
		n	(%)	n	(%)	n	(%)	n	(%)
LIVER AND BILIARY SYSTEM	TOTAL	0	.	0	.	3	0.4%	1	0.1%
	GAMMA-GT INCREASED	0	.	0	.	1	0.1%	1	0.1%
	HEPATIC ENZYMES INCREASED	0	.	0	.	2	0.3%	0	.
METABOLIC AND NUTRITIONAL	TOTAL	1	0.1%	1	0.1%	2	0.3%	6	0.9%
	HYPERGLYCEMIA	1	0.1%	0	.	2	0.3%	6	0.9%
	WEIGHT DECREASE	0	.	1	0.1%	0	.	0	.
MUSCULOSKELETAL SYSTEM	TOTAL	1	0.1%	5	0.7%	3	0.4%	12	1.7%
	ARTHRALGIA	0	.	1	0.1%	0	.	4	0.6%
	ARTHRITIS	0	.	0	.	0	.	1	0.1%
	BACK PAIN	1	0.1%	4	0.6%	3	0.4%	7	1.0%
	MYALGIA	0	.	0	.	0	.	0	.
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	TOTAL	0	.	0	.	1	0.1%	0	.
	ANGINA PECTORIS	0	.	0	.	1	0.1%	0	.
NEOPLASM	TOTAL	0	.	0	.	0	.	0	.
	NEOPLASM NOS	0	.	0	.	0	.	0	.
PSYCHIATRIC	TOTAL	1	0.1%	2	0.3%	2	0.3%	5	0.7%
	ANXIETY	0	.	0	.	1	0.1%	2	0.3%
	DEPRESSION	0	.	0	.	0	.	0	.
	INSOMNIA	1	0.1%	2	0.3%	1	0.1%	4	0.6%
REPRODUCTIVE MALE	TOTAL	0	.	1	0.1%	0	.	0	.
	PROSTATIC DISORDER	0	.	1	0.1%	0	.	0	.
RESISTANCE MECHANISM	TOTAL	0	.	1	0.1%	3	0.4%	4	0.6%
	INFECTION	0	.	0	.	0	.	1	0.1%
	INFECTION VIRAL	0	.	1	0.1%	1	0.1%	2	0.3%
	UPPER RESP TRACT INFECTION	0	.	0	.	2	0.3%	1	0.1%
RESPIRATORY SYSTEM	TOTAL	3	0.4%	41	5.7%	35	5.0%	55	7.9%
	BRONCHITIS	0	.	0	.	1	0.1%	1	0.1%

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INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		29-56		57-84		85-112		113-140	
		(N= 679)		(N= 664)		(N= 651)		(N= 638)	
		n	(%)	n	(%)	n	(%)	n	(%)
LIVER AND BILIARY SYSTEM	TOTAL	1	0.1%	0	.	4	0.6%	1	0.2%
	GAMMA-GT INCREASED	0	.	0	.	1	0.2%	1	0.2%
	HEPATIC ENZYMES INCREASED	1	0.1%	0	.	3	0.5%	0	.
METABOLIC AND NUTRITIONAL	TOTAL	2	0.3%	2	0.3%	1	0.2%	3	0.5%
	HYPERGLYCEMIA	1	0.1%	2	0.3%	1	0.2%	2	0.3%
	WEIGHT DECREASE	1	0.1%	0	.	0	.	1	0.2%
MUSCULOSKELETAL SYSTEM	TOTAL	11	1.6%	15	2.3%	6	0.9%	9	1.4%
	ARTHRALGIA	5	0.7%	3	0.5%	1	0.2%	3	0.5%
	ARTHRITIS	0	.	3	0.5%	1	0.2%	1	0.2%
	BACK PAIN	6	0.9%	7	1.1%	3	0.5%	2	0.3%
	MYALGIA	1	0.1%	2	0.3%	1	0.2%	3	0.5%
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	TOTAL	2	0.3%	1	0.2%	0	.	0	.
	ANGINA PECTORIS	2	0.3%	1	0.2%	0	.	0	.
NEOPLASM	TOTAL	0	.	0	.	0	.	0	.
	NEOPLASM NOS	0	.	0	.	0	.	0	.
PSYCHIATRIC	TOTAL	8	1.2%	6	0.9%	4	0.6%	6	0.9%
	ANXIETY	2	0.3%	3	0.5%	2	0.3%	2	0.3%
	DEPRESSION	5	0.7%	0	.	1	0.2%	2	0.3%
	INSOMNIA	1	0.1%	3	0.5%	1	0.2%	2	0.3%
REPRODUCTIVE MALE	TOTAL	0	.	1	0.2%	1	0.2%	2	0.3%
	PROSTATIC DISORDER	0	.	1	0.2%	1	0.2%	2	0.3%
RESISTANCE MECHANISM	TOTAL	14	2.1%	14	2.1%	14	2.2%	15	2.4%
	INFECTION	3	0.4%	0	.	0	.	0	.
	INFECTION VIRAL	8	1.2%	8	1.2%	6	0.9%	9	1.4%
	UPPER RESP TRACT INFECTION	4	0.6%	7	1.1%	8	1.2%	6	0.9%
RESPIRATORY SYSTEM	TOTAL	70	10.3%	63	9.5%	50	7.7%	48	7.5%
	BRONCHITIS	1	0.1%	0	.	0	.	1	0.2%

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TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		141-168 (N= 631)		169-252 (N= 625)		253-336 (N= 600)		337-420 (N= 586)	
		n	(%)	n	(%)	n	(%)	n	(%)
LIVER AND BILIARY SYSTEM	TOTAL	1	0.2%	3	0.5%	6	1.0%	0	.
	GAMMA-GT INCREASED	1	0.2%	1	0.2%	3	0.5%	0	.
	HEPATIC ENZYMES INCREASED	0	.	2	0.3%	3	0.5%	0	.
METABOLIC AND NUTRITIONAL	TOTAL	4	0.6%	7	1.1%	5	0.8%	2	0.3%
	HYPERGLYCEMIA	2	0.3%	5	0.8%	3	0.5%	1	0.2%
	WEIGHT DECREASE	2	0.3%	2	0.3%	2	0.3%	1	0.2%
MUSCULOSKELETAL SYSTEM	TOTAL	7	1.1%	16	2.6%	14	2.3%	17	2.9%
	ARTHRALGIA	3	0.5%	3	0.5%	4	0.7%	4	0.7%
	ARTHRITIS	0	.	1	0.2%	3	0.5%	1	0.2%
	BACK PAIN	3	0.5%	7	1.1%	6	1.0%	10	1.7%
	MYALGIA	1	0.2%	5	0.8%	2	0.3%	2	0.3%
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	TOTAL	1	0.2%	2	0.3%	1	0.2%	2	0.3%
	ANGINA PECTORIS	1	0.2%	2	0.3%	1	0.2%	2	0.3%
NEOPLASM	TOTAL	0	.	8	1.3%	1	0.2%	3	0.5%
	NEOPLASM NOS	0	.	8	1.3%	1	0.2%	3	0.5%
PSYCHIATRIC	TOTAL	5	0.8%	5	0.8%	11	1.8%	4	0.7%
	ANXIETY	1	0.2%	0	.	3	0.5%	1	0.2%
	DEPRESSION	4	0.6%	0	.	7	1.2%	2	0.3%
	INSOMNIA	0	.	5	0.8%	2	0.3%	1	0.2%
REPRODUCTIVE MALE	TOTAL	0	.	3	0.5%	2	0.3%	1	0.2%
	PROSTATIC DISORDER	0	.	3	0.5%	2	0.3%	1	0.2%
RESISTANCE MECHANISM	TOTAL	4	0.6%	12	1.9%	11	1.8%	14	2.4%
	INFECTION	1	0.2%	1	0.2%	3	0.5%	3	0.5%
	INFECTION VIRAL	3	0.5%	4	0.6%	5	0.8%	4	0.7%
	UPPER RESP TRACT INFECTION	0	.	7	1.1%	5	0.8%	7	1.2%
RESPIRATORY SYSTEM	TOTAL	46	7.3%	77	12.3%	66	11.0%	57	9.7%
	BRONCHITIS	1	0.2%	0	.	4	0.7%	2	0.3%

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PROTOCOL 040

PRIOR TREATMENT: TOTAL

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		421-504 (N= 551)		505-588 (N= 533)		589-672 (N= 505)		673-756 (N= 489)	
		n	(%)	n	(%)	n	(%)	n	(%)
LIVER AND BILIARY SYSTEM	TOTAL	4	0.7%	2	0.4%	2	0.4%	1	0.2%
	GAMMA-GT INCREASED	3	0.5%	1	0.2%	1	0.2%	0	.
	HEPATIC ENZYMES INCREASED	1	0.2%	1	0.2%	1	0.2%	1	0.2%
METABOLIC AND NUTRITIONAL	TOTAL	5	0.9%	2	0.4%	2	0.4%	5	1.0%
	HYPERGLYCEMIA	1	0.2%	1	0.2%	1	0.2%	2	0.4%
	WEIGHT DECREASE	4	0.7%	1	0.2%	1	0.2%	3	0.6%
MUSCULOSKELETAL SYSTEM	TOTAL	17	3.1%	11	2.1%	11	2.2%	9	1.8%
	ARTHRALGIA	6	1.1%	5	0.9%	2	0.4%	2	0.4%
	ARTHRITIS	1	0.2%	0	.	5	1.0%	1	0.2%
	BACK PAIN	9	1.6%	4	0.8%	2	0.4%	3	0.6%
	MYALGIA	2	0.4%	2	0.4%	2	0.4%	3	0.6%
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	TOTAL	5	0.9%	2	0.4%	1	0.2%	0	.
	ANGINA PECTORIS	5	0.9%	2	0.4%	1	0.2%	0	.
NEOPLASM	TOTAL	1	0.2%	1	0.2%	1	0.2%	2	0.4%
	NEOPLASM NOS	1	0.2%	1	0.2%	1	0.2%	2	0.4%
PSYCHIATRIC	TOTAL	6	1.1%	4	0.8%	6	1.2%	4	0.8%
	ANXIETY	2	0.4%	3	0.6%	2	0.4%	0	.
	DEPRESSION	2	0.4%	1	0.2%	3	0.6%	2	0.4%
	INSOMNIA	2	0.4%	0	.	2	0.4%	2	0.4%
REPRODUCTIVE MALE	TOTAL	1	0.2%	3	0.6%	0	.	1	0.2%
	PROSTATIC DISORDER	1	0.2%	3	0.6%	0	.	1	0.2%
RESISTANCE MECHANISM	TOTAL	13	2.4%	7	1.3%	8	1.6%	4	0.8%
	INFECTION	3	0.5%	1	0.2%	1	0.2%	0	.
	INFECTION VIRAL	2	0.4%	1	0.2%	2	0.4%	2	0.4%
	UPPER RESP TRACT INFECTION	8	1.5%	5	0.9%	5	1.0%	2	0.4%
RESPIRATORY SYSTEM	TOTAL	59	10.7%	35	6.6%	12	2.4%	19	3.9%
	BRONCHITIS	3	0.5%	1	0.2%	3	0.6%	1	0.2%

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3. ONLY EVENTS OCCURRING IN AT LEAST 2% OF PATIENTS ENROLLED TO SB 207499 ARE INCLUDED
4. EVENTS FOR WHICH THE ONSET IS UNDETERMINED ARE ASSUMED TO HAVE OCCURRED AT DAY 1

TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		757-840 (N= 399)		841-924 (N= 263)		925-1008 (N= 77)		1009-1092 (N= 0)	
		n	(%)	n	(%)	n	(%)	n	(%)
LIVER AND BILIARY SYSTEM	TOTAL	1	0.3%	1	0.4%	0	.	0	.
	GAMMA-GT INCREASED	1	0.3%	1	0.4%	0	.	0	.
	HEPATIC ENZYMES INCREASED	0	.	0	.	0	.	0	.
METABOLIC AND NUTRITIONAL	TOTAL	1	0.3%	0	.	0	.	0	.
	HYPERGLYCEMIA	0	.	0	.	0	.	0	.
	WEIGHT DECREASE	1	0.3%	0	.	0	.	0	.
MUSCULOSKELETAL SYSTEM	TOTAL	4	1.0%	2	0.8%	0	.	0	.
	ARTHRALGIA	3	0.8%	1	0.4%	0	.	0	.
	ARTHRITIS	1	0.3%	0	.	0	.	0	.
	BACK PAIN	1	0.3%	1	0.4%	0	.	0	.
	MYALGIA	0	.	0	.	0	.	0	.
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	TOTAL	0	.	0	.	0	.	0	.
	ANGINA PECTORIS	0	.	0	.	0	.	0	.
NEOPLASM	TOTAL	0	.	2	0.8%	0	.	0	.
	NEOPLASM NOS	0	.	2	0.8%	0	.	0	.
PSYCHIATRIC	TOTAL	4	1.0%	1	0.4%	0	.	0	.
	ANXIETY	1	0.3%	0	.	0	.	0	.
	DEPRESSION	1	0.3%	1	0.4%	0	.	0	.
	INSOMNIA	2	0.5%	0	.	0	.	0	.
REPRODUCTIVE MALE	TOTAL	1	0.3%	0	.	0	.	0	.
	PROSTATIC DISORDER	1	0.3%	0	.	0	.	0	.
RESISTANCE MECHANISM	TOTAL	5	1.3%	1	0.4%	0	.	0	.
	INFECTION	0	.	0	.	0	.	0	.
	INFECTION VIRAL	2	0.5%	0	.	0	.	0	.
	UPPER RESP TRACT INFECTION	3	0.8%	1	0.4%	0	.	0	.
RESPIRATORY SYSTEM	TOTAL	16	4.0%	8	3.0%	0	.	0	.
	BRONCHITIS	3	0.8%	0	.	0	.	0	.

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4. EVENTS FOR WHICH THE ONSET IS UNDETERMINED ARE ASSUMED TO HAVE OCCURRED AT DAY 1

TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE			
		1093-1176 (N= 0)		TOTAL (N= 723)	
		n	(%)	n	(%)
LIVER AND BILIARY SYSTEM	TOTAL	0	.	30	4.1%
	GAMMA-GT INCREASED	0	.	16	2.2%
	HEPATIC ENZYMES INCREASED	0	.	15	2.1%
METABOLIC AND NUTRITIONAL	TOTAL	0	.	51	7.1%
	HYPERGLYCEMIA	0	.	31	4.3%
	WEIGHT DECREASE	0	.	20	2.8%
MUSCULOSKELETAL SYSTEM	TOTAL	0	.	146	20.2%
	ARTHRALGIA	0	.	50	6.9%
	ARTHRITIS	0	.	19	2.6%
	BACK PAIN	0	.	79	10.9%
	MYALGIA	0	.	26	3.6%
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	TOTAL	0	.	18	2.5%
	ANGINA PECTORIS	0	.	18	2.5%
NEOPLASM	TOTAL	0	.	19	2.6%
	NEOPLASM NOS	0	.	19	2.6%
PSYCHIATRIC	TOTAL	0	.	74	10.2%
	ANXIETY	0	.	25	3.5%
	DEPRESSION	0	.	31	4.3%
	INSOMNIA	0	.	31	4.3%
REPRODUCTIVE MALE	TOTAL	0	.	17	2.4%
	PROSTATIC DISORDER	0	.	17	2.4%
RESISTANCE MECHANISM	TOTAL	0	.	132	18.3%
	INFECTION	0	.	17	2.4%
	INFECTION VIRAL	0	.	60	8.3%
	UPPER RESP TRACT INFECTION	0	.	71	9.8%
RESPIRATORY SYSTEM	TOTAL	0	.	524	72.5%
	BRONCHITIS	0	.	22	3.0%

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TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		1		2-7		8-14		15-28	
		(N= 723)		(N= 721)		(N= 705)		(N= 692)	
		n	(%)	n	(%)	n	(%)	n	(%)
RESPIRATORY SYSTEM	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	1	0.1%	30	4.2%	27	3.8%	43	6.2%
	COUGHING	1	0.1%	2	0.3%	1	0.1%	2	0.3%
	DYSPNEA	0	.	0	.	1	0.1%	2	0.3%
	PHARYNGITIS	1	0.1%	2	0.3%	1	0.1%	3	0.4%
	PNEUMONIA	0	.	0	.	0	.	0	.
	RESPIRATORY DISORDER	0	.	1	0.1%	0	.	4	0.6%
	RHINITIS	1	0.1%	5	0.7%	3	0.4%	3	0.4%
	SINUSITIS	0	.	1	0.1%	1	0.1%	2	0.3%
SKIN AND APPENDAGES	TOTAL	0	.	0	.	1	0.1%	1	0.1%
	PRURITUS	0	.	0	.	1	0.1%	1	0.1%
URINARY SYSTEM	TOTAL	2	0.3%	2	0.3%	3	0.4%	3	0.4%
	ALBUMINURIA	0	.	0	.	2	0.3%	0	.
	HEMATURIA	0	.	2	0.3%	1	0.1%	2	0.3%
	PYURIA	1	0.1%	1	0.1%	0	.	0	.
	URINARY TRACT INFECTION	1	0.1%	0	.	0	.	1	0.1%
VISION	TOTAL	0	.	0	.	0	.	2	0.3%
	CONJUNCTIVITIS	0	.	0	.	0	.	2	0.3%
WHITE CELL AND RETICULOENDOTHELIAL SYSTE	TOTAL	0	.	1	0.1%	1	0.1%	2	0.3%
	LEUKOCYTOSIS	0	.	1	0.1%	1	0.1%	2	0.3%

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TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		29-56 (N= 679)		57-84 (N= 664)		85-112 (N= 651)		113-140 (N= 638)	
		n	(%)	n	(%)	n	(%)	n	(%)
RESPIRATORY SYSTEM	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	52	7.7%	49	7.4%	34	5.2%	37	5.8%
	COUGHING	4	0.6%	2	0.3%	4	0.6%	3	0.5%
	DYSPNEA	0	.	1	0.2%	0	.	0	.
	PHARYNGITIS	7	1.0%	3	0.5%	4	0.6%	4	0.6%
	PNEUMONIA	1	0.1%	3	0.5%	3	0.5%	1	0.2%
	RESPIRATORY DISORDER	2	0.3%	1	0.2%	3	0.5%	1	0.2%
	RHINITIS	5	0.7%	4	0.6%	2	0.3%	3	0.5%
	SINUSITIS	2	0.3%	1	0.2%	2	0.3%	0	.
SKIN AND APPENDAGES	TOTAL	2	0.3%	3	0.5%	1	0.2%	1	0.2%
	PRURITUS	2	0.3%	3	0.5%	1	0.2%	1	0.2%
URINARY SYSTEM	TOTAL	6	0.9%	8	1.2%	4	0.6%	4	0.6%
	ALBUMINURIA	0	.	0	.	0	.	2	0.3%
	HEMATURIA	2	0.3%	2	0.3%	1	0.2%	1	0.2%
	PYURIA	0	.	3	0.5%	2	0.3%	1	0.2%
	URINARY TRACT INFECTION	4	0.6%	3	0.5%	2	0.3%	0	.
VISION	TOTAL	1	0.1%	0	.	0	.	1	0.2%
	CONJUNCTIVITIS	1	0.1%	0	.	0	.	1	0.2%
WHITE CELL AND RETICULOENDOTHELIAL SYSTE	TOTAL	2	0.3%	1	0.2%	1	0.2%	1	0.2%
	LEUKOCYTOSIS	2	0.3%	1	0.2%	1	0.2%	1	0.2%

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TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		141-168 (N= 631)		169-252 (N= 625)		253-336 (N= 600)		337-420 (N= 586)	
		n	(%)	n	(%)	n	(%)	n	(%)
RESPIRATORY SYSTEM	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	29	4.6%	56	9.0%	32	5.3%	32	5.5%
	COUGHING	3	0.5%	2	0.3%	4	0.7%	4	0.7%
	DYSPNEA	2	0.3%	2	0.3%	3	0.5%	1	0.2%
	PHARYNGITIS	2	0.3%	2	0.3%	9	1.5%	6	1.0%
	PNEUMONIA	3	0.5%	1	0.2%	0	.	3	0.5%
	RESPIRATORY DISORDER	2	0.3%	2	0.3%	10	1.7%	4	0.7%
	RHINITIS	6	1.0%	12	1.9%	7	1.2%	3	0.5%
	SINUSITIS	1	0.2%	4	0.6%	4	0.7%	3	0.5%
SKIN AND APPENDAGES	TOTAL	0	.	3	0.5%	2	0.3%	0	.
	PRURITUS	0	.	3	0.5%	2	0.3%	0	.
URINARY SYSTEM	TOTAL	5	0.8%	11	1.8%	10	1.7%	13	2.2%
	ALBUMINURIA	3	0.5%	1	0.2%	3	0.5%	3	0.5%
	HEMATURIA	0	.	3	0.5%	5	0.8%	2	0.3%
	PYURIA	2	0.3%	0	.	0	.	2	0.3%
	URINARY TRACT INFECTION	0	.	7	1.1%	2	0.3%	8	1.4%
VISION	TOTAL	0	.	2	0.3%	2	0.3%	0	.
	CONJUNCTIVITIS	0	.	2	0.3%	2	0.3%	0	.
WHITE CELL AND RETICULOENDOTHELIAL SYSTE	TOTAL	0	.	1	0.2%	4	0.7%	3	0.5%
	LEUKOCYTOSIS	0	.	1	0.2%	4	0.7%	3	0.5%

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TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		421-504 (N= 551)		505-588 (N= 533)		589-672 (N= 505)		673-756 (N= 489)	
		n	(%)	n	(%)	n	(%)	n	(%)
RESPIRATORY SYSTEM	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	28	5.1%	13	2.4%	2	0.4%	7	1.4%
	COUGHING	5	0.9%	2	0.4%	1	0.2%	2	0.4%
	DYSPNEA	2	0.4%	2	0.4%	0	.	2	0.4%
	PHARYNGITIS	3	0.5%	7	1.3%	1	0.2%	1	0.2%
	PNEUMONIA	2	0.4%	3	0.6%	1	0.2%	2	0.4%
	RESPIRATORY DISORDER	5	0.9%	0	.	1	0.2%	2	0.4%
	RHINITIS	6	1.1%	5	0.9%	3	0.6%	2	0.4%
	SINUSITIS	5	0.9%	2	0.4%	0	.	0	.
SKIN AND APPENDAGES	TOTAL	1	0.2%	0	.	2	0.4%	1	0.2%
	PRURITUS	1	0.2%	0	.	2	0.4%	1	0.2%
URINARY SYSTEM	TOTAL	5	0.9%	3	0.6%	3	0.6%	2	0.4%
	ALBUMINURIA	2	0.4%	0	.	0	.	0	.
	HEMATURIA	1	0.2%	2	0.4%	1	0.2%	0	.
	PYURIA	1	0.2%	1	0.2%	1	0.2%	1	0.2%
	URINARY TRACT INFECTION	2	0.4%	0	.	1	0.2%	1	0.2%
VISION	TOTAL	3	0.5%	1	0.2%	2	0.4%	0	.
	CONJUNCTIVITIS	3	0.5%	1	0.2%	2	0.4%	0	.
WHITE CELL AND RETICULOENDOTHELIAL SYSTE	TOTAL	1	0.2%	0	.	2	0.4%	3	0.6%
	LEUKOCYTOSIS	1	0.2%	0	.	2	0.4%	3	0.6%

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TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL

WHO BODY SYSTEM	WHO PREFERRED TERM	DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE							
		757-840 (N= 399)		841-924 (N= 263)		925-1008 (N= 77)		1009-1092 (N= 0)	
		n	(%)	n	(%)	n	(%)	n	(%)
RESPIRATORY SYSTEM	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	6	1.5%	4	1.5%	0	.	0	.
	COUGHING	1	0.3%	1	0.4%	0	.	0	.
	DYSPNEA	2	0.5%	1	0.4%	0	.	0	.
	PHARYNGITIS	1	0.3%	0	.	0	.	0	.
	PNEUMONIA	1	0.3%	0	.	0	.	0	.
	RESPIRATORY DISORDER	0	.	0	.	0	.	0	.
	RHINITIS	1	0.3%	1	0.4%	0	.	0	.
	SINUSITIS	1	0.3%	1	0.4%	0	.	0	.
SKIN AND APPENDAGES	TOTAL	0	.	0	.	0	.	0	.
	PRURITUS	0	.	0	.	0	.	0	.
URINARY SYSTEM	TOTAL	0	.	2	0.8%	0	.	0	.
	ALBUMINURIA	0	.	1	0.4%	0	.	0	.
	HEMATURIA	0	.	1	0.4%	0	.	0	.
	PYURIA	0	.	0	.	0	.	0	.
	URINARY TRACT INFECTION	0	.	0	.	0	.	0	.
VISION	TOTAL	1	0.3%	0	.	0	.	0	.
	CONJUNCTIVITIS	1	0.3%	0	.	0	.	0	.
WHITE CELL AND RETICULOENDOTHELIAL SYSTE	TOTAL	0	.	0	.	0	.	0	.
	LEUKOCYTOSIS	0	.	0	.	0	.	0	.

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TABLE 15.5

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES ($\geq 2\%$) BY INITIAL TIME OF ONSET, BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT: TOTAL

		DAYS RELATIVE TO FIRST STUDY MEDICATION DOSE			
		1093-1176 (N= 0)		TOTAL (N= 723)	
WHO BODY SYSTEM	WHO PREFERRED TERM	n	(%)	n	(%)
RESPIRATORY SYSTEM	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	0	.	482	66.7%
	COUGHING	0	.	44	6.1%
	DYSPNEA	0	.	21	2.9%
	PHARYNGITIS	0	.	57	7.9%
	PNEUMONIA	0	.	24	3.3%
	RESPIRATORY DISORDER	0	.	38	5.3%
	RHINITIS	0	.	72	10.0%
	SINUSITIS	0	.	30	4.1%
SKIN AND APPENDAGES	TOTAL	0	.	18	2.5%
	PRURITUS	0	.	18	2.5%
URINARY SYSTEM	TOTAL	0	.	73	10.1%
	ALBUMINURIA	0	.	17	2.4%
	HEMATURIA	0	.	26	3.6%
	PYURIA	0	.	16	2.2%
	URINARY TRACT INFECTION	0	.	32	4.4%
VISION	TOTAL	0	.	15	2.1%
	CONJUNCTIVITIS	0	.	15	2.1%
WHITE CELL AND RETICULOENDOTHELIAL SYSTE	TOTAL	0	.	23	3.2%
	LEUKOCYTOSIS	0	.	23	3.2%

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TABLE 15.6

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES THAT LED TO DOSE INTERRUPTION BY BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
TOTAL	TOTAL	36 (14.8%)	61 (12.7%)	97 (13.4%)
APPLICATION SITE	TOTAL	0 .	1 (0.2%)	1 (0.1%)
	OTITIS EXTERNA	0 .	1 (0.2%)	1 (0.1%)
AUTONOMIC NERVOUS SYSTEM	TOTAL	1 (0.4%)	0 .	1 (0.1%)
	SWEATING INCREASED	1 (0.4%)	0 .	1 (0.1%)
BODY AS A WHOLE GENERAL	TOTAL	2 (0.8%)	4 (0.8%)	6 (0.8%)
	ALLERGIC REACTION	1 (0.4%)	0 .	1 (0.1%)
	INJURY	1 (0.4%)	4 (0.8%)	5 (0.7%)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	TOTAL	2 (0.8%)	3 (0.6%)	5 (0.7%)
	CONVULSIONS	0 .	1 (0.2%)	1 (0.1%)
	DIZZINESS	1 (0.4%)	1 (0.2%)	2 (0.3%)
	HEADACHE	1 (0.4%)	1 (0.2%)	2 (0.3%)
GASTROINTESTINAL SYSTEM	TOTAL	21 (8.6%)	28 (5.8%)	49 (6.8%)
	ABDOMINAL PAIN	6 (2.5%)	8 (1.7%)	14 (1.9%)
	ANOREXIA	0 .	1 (0.2%)	1 (0.1%)
	CONSTIPATION	0 .	1 (0.2%)	1 (0.1%)
	DIARRHEA	4 (1.6%)	8 (1.7%)	12 (1.7%)
	DYSPEPSIA	2 (0.8%)	4 (0.8%)	6 (0.8%)
	DYSPHAGIA	0 .	1 (0.2%)	1 (0.1%)
	FLATULENCE	1 (0.4%)	0 .	1 (0.1%)
	GASTRIC ULCER	0 .	1 (0.2%)	1 (0.1%)
	GASTROENTERITIS	4 (1.6%)	3 (0.6%)	7 (1.0%)
	GASTROINTESTINAL DISORDER NOS	1 (0.4%)	0 .	1 (0.1%)
	GI HEMORRHAGE	1 (0.4%)	0 .	1 (0.1%)
	INTESTINAL OBSTRUCTION	1 (0.4%)	2 (0.4%)	3 (0.4%)
	MELENA	0 .	1 (0.2%)	1 (0.1%)
	NAUSEA	3 (1.2%)	4 (0.8%)	7 (1.0%)
	TOOTH CARIES	1 (0.4%)	0 .	1 (0.1%)
	VOMITING	0 .	3 (0.6%)	3 (0.4%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM/PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AN ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 15.6

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES THAT LED TO DOSE INTERRUPTION BY BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
HEART RATE AND RHYTHM	TOTAL	1 (0.4%)	2 (0.4%)	3 (0.4%)
	ARRHYTHMIA	1 (0.4%)	0	1 (0.1%)
	CARDIAC ARREST	0	1 (0.2%)	1 (0.1%)
	PALPITATION	0	1 (0.2%)	1 (0.1%)
	TACHYCARDIA	0	1 (0.2%)	1 (0.1%)
LIVER AND BILIARY SYSTEM	TOTAL	0	2 (0.4%)	2 (0.3%)
	CHOLECYSTITIS	0	1 (0.2%)	1 (0.1%)
	LIVER FATTY	0	1 (0.2%)	1 (0.1%)
METABOLIC AND NUTRITIONAL	TOTAL	1 (0.4%)	0	1 (0.1%)
	HYPERNATREMIA	1 (0.4%)	0	1 (0.1%)
MUSCULOSKELETAL SYSTEM	TOTAL	1 (0.4%)	2 (0.4%)	3 (0.4%)
	ARTHROPATHY	1 (0.4%)	1 (0.2%)	2 (0.3%)
	MYALGIA	0	1 (0.2%)	1 (0.1%)
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	TOTAL	0	3 (0.6%)	3 (0.4%)
	ANGINA PECTORIS	0	2 (0.4%)	2 (0.3%)
	ANGINA PECTORIS AGGRAVATED	0	1 (0.2%)	1 (0.1%)
NEOPLASM	TOTAL	1 (0.4%)	0	1 (0.1%)
	NEOPLASM NOS	1 (0.4%)	0	1 (0.1%)
PSYCHIATRIC	TOTAL	0	2 (0.4%)	2 (0.3%)
	CONFUSION	0	1 (0.2%)	1 (0.1%)
	DEPRESSION	0	1 (0.2%)	1 (0.1%)
REPRODUCTIVE MALE	TOTAL	0	1 (0.2%)	1 (0.1%)
	PROSTATIC DISORDER	0	1 (0.2%)	1 (0.1%)
RESISTANCE MECHANISM	TOTAL	2 (0.8%)	1 (0.2%)	3 (0.4%)
	HERPES ZOSTER	1 (0.4%)	0	1 (0.1%)

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TABLE 15.6

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES THAT LED TO DOSE INTERRUPTION BY BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
RESISTANCE MECHANISM	INFECTION	0 .	1 (0.2%)	1 (0.1%)
	SEPSIS	1 (0.4%)	0 .	1 (0.1%)
RESPIRATORY SYSTEM	TOTAL	12 (4.9%)	23 (4.8%)	35 (4.8%)
	BRONCHITIS	0 .	2 (0.4%)	2 (0.3%)
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	9 (3.7%)	18 (3.8%)	27 (3.7%)
	PLEURISY	0 .	1 (0.2%)	1 (0.1%)
	PNEUMONIA	3 (1.2%)	3 (0.6%)	6 (0.8%)
	RESPIRATORY DISORDER	2 (0.8%)	1 (0.2%)	3 (0.4%)
SKIN AND APPENDAGES	TOTAL	1 (0.4%)	0 .	1 (0.1%)
	URTICARIA	1 (0.4%)	0 .	1 (0.1%)
URINARY SYSTEM	TOTAL	1 (0.4%)	4 (0.8%)	5 (0.7%)
	DYSURIA	0 .	1 (0.2%)	1 (0.1%)
	HEMATURIA	1 (0.4%)	0 .	1 (0.1%)
	PYELONEPHRITIS	0 .	1 (0.2%)	1 (0.1%)
	RENAL FAILURE ACUTE	0 .	1 (0.2%)	1 (0.1%)
	URINARY RETENTION	0 .	2 (0.4%)	2 (0.3%)
VASCULAR EXTRACARDIAC	TOTAL	0 .	1 (0.2%)	1 (0.1%)
	CEREBROVASCULAR DISORDER	0 .	1 (0.2%)	1 (0.1%)
VISION	TOTAL	1 (0.4%)	0 .	1 (0.1%)
	CATARACT	1 (0.4%)	0 .	1 (0.1%)

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TABLE 15.7

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES THAT REQUIRED CORRECTIVE THERAPY BY BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
TOTAL	TOTAL	197 (81.1%)	408 (85.0%)	605 (83.7%)
APPLICATION SITE	TOTAL	3 (1.2%)	5 (1.0%)	8 (1.1%)
	INJECTION SITE	0 .	1 (0.2%)	1 (0.1%)
	INFLAMMATION			
	OTITIS EXTERNA	3 (1.2%)	5 (1.0%)	8 (1.1%)
	TYMPANIC MEMBRANE PERFORATION	0 .	1 (0.2%)	1 (0.1%)
AUTONOMIC NERVOUS SYSTEM	TOTAL	2 (0.8%)	1 (0.2%)	3 (0.4%)
	MOUTH DRY	1 (0.4%)	1 (0.2%)	2 (0.3%)
	SWEATING INCREASED	1 (0.4%)	0 .	1 (0.1%)
BODY AS A WHOLE GENERAL	TOTAL	46 (18.9%)	90 (18.8%)	136 (18.8%)
	ALLERGIC REACTION	2 (0.8%)	2 (0.4%)	4 (0.6%)
	ASTHENIA	2 (0.8%)	4 (0.8%)	6 (0.8%)
	CELLULITIS	1 (0.4%)	4 (0.8%)	5 (0.7%)
	CHEST PAIN	11 (4.5%)	17 (3.5%)	28 (3.9%)
	CHEST PAIN PRECORDIAL	2 (0.8%)	1 (0.2%)	3 (0.4%)
	CHEST PAIN SUBSTERNAL	1 (0.4%)	0 .	1 (0.1%)
	EDEMA	0 .	1 (0.2%)	1 (0.1%)
	EDEMA DEPENDENT	1 (0.4%)	3 (0.6%)	4 (0.6%)
	EDEMA LEGS	4 (1.6%)	4 (0.8%)	8 (1.1%)
	FATIGUE	2 (0.8%)	0 .	2 (0.3%)
	FEVER	6 (2.5%)	6 (1.3%)	12 (1.7%)
	HOT FLUSHES	1 (0.4%)	0 .	1 (0.1%)
	INFLUENZA-LIKE SYMPTOMS	1 (0.4%)	2 (0.4%)	3 (0.4%)
	INJURY	18 (7.4%)	47 (9.8%)	65 (9.0%)
	MALAISE	3 (1.2%)	0 .	3 (0.4%)
	PAIN	3 (1.2%)	15 (3.1%)	18 (2.5%)
	THERAPEUTIC RESPONSE INCREASED	0 .	2 (0.4%)	2 (0.3%)
CARDIOVASCULAR GENERAL	TOTAL	12 (4.9%)	37 (7.7%)	49 (6.8%)
	ANEURYSM	1 (0.4%)	2 (0.4%)	3 (0.4%)
	CARDIAC FAILURE	2 (0.8%)	3 (0.6%)	5 (0.7%)
	COR PULMONALE	0 .	1 (0.2%)	1 (0.1%)

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TABLE 15.7

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES THAT REQUIRED CORRECTIVE THERAPY BY BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
CARDIOVASCULAR GENERAL	HEART VALVE DISORDERS	1 (0.4%)	0 .	1 (0.1%)
	HYPERTENSION	5 (2.1%)	25 (5.2%)	30 (4.1%)
	HYPERTENSION AGGRAVATED	3 (1.2%)	4 (0.8%)	7 (1.0%)
	HYPERTENSION PULMONARY	0 .	1 (0.2%)	1 (0.1%)
	HYPOTENSION POSTURAL	0 .	1 (0.2%)	1 (0.1%)
	SYNCOPE	0 .	2 (0.4%)	2 (0.3%)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	TOTAL	33 (13.6%)	47 (9.8%)	80 (11.1%)
	ATAXIA	1 (0.4%)	0 .	1 (0.1%)
	CONVULSIONS	0 .	1 (0.2%)	1 (0.1%)
	DIZZINESS	3 (1.2%)	5 (1.0%)	8 (1.1%)
	DYSPHONIA	1 (0.4%)	1 (0.2%)	2 (0.3%)
	EXTRAPYRAMIDAL DISORDER	0 .	1 (0.2%)	1 (0.1%)
	HEADACHE	18 (7.4%)	20 (4.2%)	38 (5.3%)
	HYPERTONIA	1 (0.4%)	2 (0.4%)	3 (0.4%)
	MIGRAINE	1 (0.4%)	2 (0.4%)	3 (0.4%)
	MUSCLE CONTRACTIONS INVOLUNTARY	1 (0.4%)	2 (0.4%)	3 (0.4%)
	NERVE ROOT LESION	0 .	1 (0.2%)	1 (0.1%)
	NEURALGIA	7 (2.9%)	11 (2.3%)	18 (2.5%)
	NEUROPATHY	0 .	1 (0.2%)	1 (0.1%)
	NEUROPATHY PERIPHERAL	0 .	2 (0.4%)	2 (0.3%)
	PARESTHESIA	2 (0.8%)	1 (0.2%)	3 (0.4%)
	PARKINSONISM AGGRAVATED	0 .	1 (0.2%)	1 (0.1%)
	TREMOR	1 (0.4%)	0 .	1 (0.1%)
	TRIGEMINAL NEURALGIA	1 (0.4%)	0 .	1 (0.1%)
	VERTIGO	2 (0.8%)	5 (1.0%)	7 (1.0%)
	WITHDRAWAL HEADACHE	0 .	1 (0.2%)	1 (0.1%)
COLLAGEN	TOTAL	0 .	3 (0.6%)	3 (0.4%)
	ARTHRITIS RHEUMATOID	0 .	2 (0.4%)	2 (0.3%)
	ARTHRITIS RHEUMATOID AGGRAVATED	0 .	1 (0.2%)	1 (0.1%)
ENDOCRINE	TOTAL	2 (0.8%)	8 (1.7%)	10 (1.4%)

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SB 207499

TABLE 15.7

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES THAT REQUIRED CORRECTIVE THERAPY BY BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
ENDOCRINE	GOITRE	0	1 (0.2%)	1 (0.1%)
	HYPERTHYROIDISM	1 (0.4%)	5 (1.0%)	6 (0.8%)
	HYPOTHYROIDISM	0	3 (0.6%)	3 (0.4%)
	SIALOADENITIS	1 (0.4%)	0	1 (0.1%)
	THYROIDITIS	1 (0.4%)	0	1 (0.1%)
GASTROINTESTINAL SYSTEM	TOTAL	70 (28.8%)	109 (22.7%)	179 (24.8%)
	ABDOMINAL PAIN	22 (9.1%)	31 (6.5%)	53 (7.3%)
	ANOREXIA	1 (0.4%)	1 (0.2%)	2 (0.3%)
	ANUS DISORDER	0	2 (0.4%)	2 (0.3%)
	COLITIS	0	1 (0.2%)	1 (0.1%)
	CONSTIPATION	4 (1.6%)	12 (2.5%)	16 (2.2%)
	DIARRHEA	13 (5.3%)	15 (3.1%)	28 (3.9%)
	DIARRHEA BLOODY	0	1 (0.2%)	1 (0.1%)
	DIVERTICULITIS	0	2 (0.4%)	2 (0.3%)
	DUODENAL ULCER	0	1 (0.2%)	1 (0.1%)
	DUODENITIS	0	2 (0.4%)	2 (0.3%)
	DYSPEPSIA	16 (6.6%)	27 (5.6%)	43 (5.9%)
	DYSPHAGIA	0	3 (0.6%)	3 (0.4%)
	ENTERITIS	1 (0.4%)	0	1 (0.1%)
	ESOPHAGITIS	1 (0.4%)	5 (1.0%)	6 (0.8%)
	ESOPHAGOSPASM	1 (0.4%)	0	1 (0.1%)
	FLATULENCE	2 (0.8%)	4 (0.8%)	6 (0.8%)
	GASTRIC ULCER	0	2 (0.4%)	2 (0.3%)
	GASTRITIS	3 (1.2%)	10 (2.1%)	13 (1.8%)
	GASTROENTERITIS	9 (3.7%)	8 (1.7%)	17 (2.4%)
	GASTROESOPHAGEAL REFLUX	2 (0.8%)	2 (0.4%)	4 (0.6%)
	GASTROINTESTINAL DISORDER NOS	2 (0.8%)	7 (1.5%)	9 (1.2%)
	GI HEMORRHAGE	3 (1.2%)	1 (0.2%)	4 (0.6%)
	GINGIVITIS	0	1 (0.2%)	1 (0.1%)
	HEMORRHAGE RECTUM	0	1 (0.2%)	1 (0.1%)
	HEMORRHOIDS	1 (0.4%)	5 (1.0%)	6 (0.8%)
	ILEUS	0	1 (0.2%)	1 (0.1%)
	INTESTINAL OBSTRUCTION	1 (0.4%)	2 (0.4%)	3 (0.4%)
	IRRITABLE BOWEL SYNDROME	1 (0.4%)	1 (0.2%)	2 (0.3%)
	MEGACOLON ACQUIRED	0	1 (0.2%)	1 (0.1%)
	MELENA	1 (0.4%)	1 (0.2%)	2 (0.3%)

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TABLE 15.7

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES THAT REQUIRED CORRECTIVE THERAPY BY BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
GASTROINTESTINAL SYSTEM	NAUSEA	5 (2.1%)	9 (1.9%)	14 (1.9%)
	PANCREATITIS	1 (0.4%)	1 (0.2%)	2 (0.3%)
	PERIODONTITIS	4 (1.6%)	12 (2.5%)	16 (2.2%)
	PERITONITIS	0 .	1 (0.2%)	1 (0.1%)
	STOMATITIS	0 .	2 (0.4%)	2 (0.3%)
	TENESMUS	0 .	1 (0.2%)	1 (0.1%)
	TONGUE EDEMA	0 .	1 (0.2%)	1 (0.1%)
	TOOTH ACHE	2 (0.8%)	6 (1.3%)	8 (1.1%)
	TOOTH CARIES	2 (0.8%)	0 .	2 (0.3%)
	TOOTH DISORDER	1 (0.4%)	1 (0.2%)	2 (0.3%)
	VOMITING	0 .	6 (1.3%)	6 (0.8%)
HEARING AND VESTIBULAR	TOTAL	6 (2.5%)	9 (1.9%)	15 (2.1%)
	DEAFNESS	1 (0.4%)	2 (0.4%)	3 (0.4%)
	EAR DISORDER NOS	3 (1.2%)	3 (0.6%)	6 (0.8%)
	EARACHE	1 (0.4%)	2 (0.4%)	3 (0.4%)
	HEARING DECREASED	0 .	1 (0.2%)	1 (0.1%)
	TINNITUS	0 .	1 (0.2%)	1 (0.1%)
	VESTIBULAR DISORDER	1 (0.4%)	1 (0.2%)	2 (0.3%)
HEART RATE AND RHYTHM	TOTAL	6 (2.5%)	18 (3.8%)	24 (3.3%)
	ARRHYTHMIA	2 (0.8%)	0 .	2 (0.3%)
	ARRHYTHMIA ATRIAL	1 (0.4%)	3 (0.6%)	4 (0.6%)
	CARDIAC ARREST	0 .	1 (0.2%)	1 (0.1%)
	EXTRASYSTOLES	1 (0.4%)	1 (0.2%)	2 (0.3%)
	FIBRILLATION ATRIAL	2 (0.8%)	8 (1.7%)	10 (1.4%)
	PALPITATION	0 .	2 (0.4%)	2 (0.3%)
	TACHYCARDIA	0 .	4 (0.8%)	4 (0.6%)
	TACHYCARDIA SUPRAVENTRICULAR	0 .	1 (0.2%)	1 (0.1%)
	TOTAL	2 (0.8%)	8 (1.7%)	10 (1.4%)
LIVER AND BILIARY SYSTEM	CHOLECYSTITIS	0 .	2 (0.4%)	2 (0.3%)
	CHOLELITHIASIS	0 .	3 (0.6%)	3 (0.4%)
	HEPATIC CIRRHOSIS	1 (0.4%)	0 .	1 (0.1%)
	HEPATIC ENZYMES INCREASED	0 .	2 (0.4%)	2 (0.3%)
	TOTAL	1 (0.4%)	5 (1.0%)	6 (0.8%)

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TABLE 15.7

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES THAT REQUIRED CORRECTIVE THERAPY BY BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
LIVER AND BILIARY SYSTEM	HEPATIC FUNCTION ABNORMAL	0 .	1 (0.2%)	1 (0.1%)
	HEPATITIS INFECTIOUS	1 (0.4%)	0 .	1 (0.1%)
	TOTAL	16 (6.6%)	30 (6.3%)	46 (6.4%)
METABOLIC AND NUTRITIONAL	DEHYDRATION	0 .	2 (0.4%)	2 (0.3%)
	DIABETES MELLITUS	2 (0.8%)	6 (1.3%)	8 (1.1%)
	DIABETES MELLITUS AGGRAVATED	0 .	3 (0.6%)	3 (0.4%)
	GLYCOSURIA	0 .	1 (0.2%)	1 (0.1%)
	GOUT	5 (2.1%)	7 (1.5%)	12 (1.7%)
	HYPERCHOLESTEROLEMIA	3 (1.2%)	3 (0.6%)	6 (0.8%)
	HYPERGLYCEMIA	1 (0.4%)	5 (1.0%)	6 (0.8%)
	HYPERLIPEMIA	0 .	3 (0.6%)	3 (0.4%)
	HYPERURICEMIA	1 (0.4%)	4 (0.8%)	5 (0.7%)
	HYPOCHLOREMIA	1 (0.4%)	0 .	1 (0.1%)
	HYPOKALEMIA	2 (0.8%)	0 .	2 (0.3%)
	HYPONATREMIA	1 (0.4%)	0 .	1 (0.1%)
	OBESITY	1 (0.4%)	0 .	1 (0.1%)
	WEIGHT DECREASE	0 .	3 (0.6%)	3 (0.4%)
	WEIGHT INCREASE	1 (0.4%)	0 .	1 (0.1%)
	TOTAL	45 (18.5%)	82 (17.1%)	127 (17.6%)
	ARTHRALGIA	17 (7.0%)	20 (4.2%)	37 (5.1%)
	ARTHRITIS	5 (2.1%)	11 (2.3%)	16 (2.2%)
MUSCULOSKELETAL SYSTEM	ARTHRITIS AGGRAVATED	1 (0.4%)	1 (0.2%)	2 (0.3%)
	ARTHROPATHY	1 (0.4%)	2 (0.4%)	3 (0.4%)
	ARTHROSIS	1 (0.4%)	3 (0.6%)	4 (0.6%)
	BACK PAIN	20 (8.2%)	42 (8.8%)	62 (8.6%)
	BONE DEVELOPMENT ABNORMAL	0 .	2 (0.4%)	2 (0.3%)
	BONE DISORDER	0 .	2 (0.4%)	2 (0.3%)
	BURSITIS	0 .	1 (0.2%)	1 (0.1%)
	DUPUYTREN'S CONTRACTURE	0 .	1 (0.2%)	1 (0.1%)
	MYALGIA	7 (2.9%)	8 (1.7%)	15 (2.1%)
	MYOSITIS	1 (0.4%)	0 .	1 (0.1%)
	OSTEOPOROSIS	1 (0.4%)	5 (1.0%)	6 (0.8%)
	SKELETAL PAIN	2 (0.8%)	5 (1.0%)	7 (1.0%)

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TABLE 15.7

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES THAT REQUIRED CORRECTIVE THERAPY BY BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
MUSCULOSKELETAL SYSTEM	TENDINITIS	0 .	2 (0.4%)	2 (0.3%)
	TENDON DISORDER	1 (0.4%)	0 .	1 (0.1%)
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	TOTAL	7 (2.9%)	16 (3.3%)	23 (3.2%)
	ANGINA PECTORIS	6 (2.5%)	10 (2.1%)	16 (2.2%)
	ANGINA PECTORIS AGGRAVATED	0 .	2 (0.4%)	2 (0.3%)
	CORONARY ARTERY DISORDER	0 .	2 (0.4%)	2 (0.3%)
	MYOCARDIAL INFARCTION	1 (0.4%)	2 (0.4%)	3 (0.4%)
	MYOCARDIAL ISCHEMIA	0 .	1 (0.2%)	1 (0.1%)
NEOPLASM	TOTAL	18 (7.4%)	20 (4.2%)	38 (5.3%)
	ADENOCARCINOMA NOS	0 .	1 (0.2%)	1 (0.1%)
	BASAL CELL CARCINOMA	1 (0.4%)	1 (0.2%)	2 (0.3%)
	BLADDER CARCINOMA	1 (0.4%)	0 .	1 (0.1%)
	BREAST NEOPLASM FEMALE	0 .	2 (0.4%)	2 (0.3%)
	CARCINOMA	3 (1.2%)	2 (0.4%)	5 (0.7%)
	COLON CARCINOMA	1 (0.4%)	0 .	1 (0.1%)
	GASTRIC CARCINOMA	1 (0.4%)	0 .	1 (0.1%)
	GI NEOPLASM MALIGNANT	0 .	1 (0.2%)	1 (0.1%)
	HEMANGIOMA ACQUIRED	0 .	1 (0.2%)	1 (0.1%)
	LIPOMA	2 (0.8%)	1 (0.2%)	3 (0.4%)
	LYMPHOMA MALIGNANT	1 (0.4%)	0 .	1 (0.1%)
	NEOPLASM MALIGNANT	1 (0.4%)	0 .	1 (0.1%)
	NEOPLASM NOS	6 (2.5%)	6 (1.3%)	12 (1.7%)
	PULMONARY CARCINOMA	1 (0.4%)	5 (1.0%)	6 (0.8%)
PLATELET BLEEDING AND CLOTTING	TOTAL	0 .	2 (0.4%)	2 (0.3%)
	HEMATOMA	0 .	1 (0.2%)	1 (0.1%)
	PURPURA	0 .	1 (0.2%)	1 (0.1%)
PSYCHIATRIC	TOTAL	25 (10.3%)	43 (9.0%)	68 (9.4%)
	AGITATION	1 (0.4%)	2 (0.4%)	3 (0.4%)
	AMNESIA	0 .	1 (0.2%)	1 (0.1%)
	ANXIETY	11 (4.5%)	10 (2.1%)	21 (2.9%)
	APATHY	1 (0.4%)	0 .	1 (0.1%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM/PREFERRED TERM
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3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 15.7

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES THAT REQUIRED CORRECTIVE THERAPY BY BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
PSYCHIATRIC	CONCENTRATION IMPAIRED	1 (0.4%)	0	1 (0.1%)
	CONFUSION	0	2 (0.4%)	2 (0.3%)
	DEPRESSION	10 (4.1%)	17 (3.5%)	27 (3.7%)
	DEPRESSION AGGRAVATED	0	1 (0.2%)	1 (0.1%)
	INSOMNIA	6 (2.5%)	18 (3.8%)	24 (3.3%)
	NERVOUSNESS	2 (0.8%)	1 (0.2%)	3 (0.4%)
RED BLOOD CELL	TOTAL	2 (0.8%)	4 (0.8%)	6 (0.8%)
	ANEMIA	1 (0.4%)	2 (0.4%)	3 (0.4%)
	ANEMIA HYPOCHROMIC	0	1 (0.2%)	1 (0.1%)
	ANEMIA MACROCYTIC	1 (0.4%)	0	1 (0.1%)
	POLYCYTHEMIA	0	1 (0.2%)	1 (0.1%)
REPRODUCTIVE FEMALE	TOTAL	1 (0.4%)	2 (0.4%)	3 (0.4%)
	PELVIC INFLAMMATION	1 (0.4%)	0	1 (0.1%)
	VAGINITIS	0	2 (0.4%)	2 (0.3%)
REPRODUCTIVE MALE	TOTAL	13 (5.3%)	11 (2.3%)	24 (3.3%)
	BALANOPOSTHITIS	1 (0.4%)	0	1 (0.1%)
	IMPOTENCE	1 (0.4%)	5 (1.0%)	6 (0.8%)
	ORCHITIS	1 (0.4%)	0	1 (0.1%)
	PENIS DISORDER	1 (0.4%)	0	1 (0.1%)
	PROSTATIC DISORDER	10 (4.1%)	6 (1.3%)	16 (2.2%)
RESISTANCE MECHANISM	TOTAL	39 (16.0%)	82 (17.1%)	121 (16.7%)
	ABSCCESS	2 (0.8%)	4 (0.8%)	6 (0.8%)
	HERPES SIMPLEX	0	2 (0.4%)	2 (0.3%)
	HERPES ZOSTER	2 (0.8%)	7 (1.5%)	9 (1.2%)
	INFECTION	6 (2.5%)	10 (2.1%)	16 (2.2%)
	INFECTION BACTERIAL	0	2 (0.4%)	2 (0.3%)
	INFECTION FUNGAL	4 (1.6%)	2 (0.4%)	6 (0.8%)
	INFECTION VIRAL	13 (5.3%)	27 (5.6%)	40 (5.5%)
	MONILIASIS	3 (1.2%)	5 (1.0%)	8 (1.1%)
	MONILIASIS GENITAL	0	1 (0.2%)	1 (0.1%)
	OTITIS MEDIA	3 (1.2%)	4 (0.8%)	7 (1.0%)
	SEPSIS	1 (0.4%)	2 (0.4%)	3 (0.4%)
	UPPER RESP TRACT INFECTION	15 (6.2%)	31 (6.5%)	46 (6.4%)
RESPIRATORY SYSTEM	TOTAL	161 (66.3%)	335 (69.8%)	496 (68.6%)

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TABLE 15.7

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES THAT REQUIRED CORRECTIVE THERAPY BY BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
RESPIRATORY SYSTEM	APNEA	1 (0.4%)	0 .	1 (0.1%)
	ASTHMA	2 (0.8%)	0 .	2 (0.3%)
	BRONCHITIS	8 (3.3%)	12 (2.5%)	20 (2.8%)
	CHEST X-RAY ABNORMAL	0 .	1 (0.2%)	1 (0.1%)
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	146 (60.1%)	311 (64.8%)	457 (63.2%)
	COUGHING	10 (4.1%)	17 (3.5%)	27 (3.7%)
	DYSPNEA	5 (2.1%)	11 (2.3%)	16 (2.2%)
	EPISTAXIS	1 (0.4%)	2 (0.4%)	3 (0.4%)
	HEMOPTYSIS	2 (0.8%)	3 (0.6%)	5 (0.7%)
	HYPOXIA	1 (0.4%)	0 .	1 (0.1%)
	LARYNGITIS	3 (1.2%)	2 (0.4%)	5 (0.7%)
	PHARYNGITIS	11 (4.5%)	28 (5.8%)	39 (5.4%)
	PLEURAL EFFUSION	1 (0.4%)	1 (0.2%)	2 (0.3%)
	PLEURISY	0 .	1 (0.2%)	1 (0.1%)
	PNEUMONIA	9 (3.7%)	13 (2.7%)	22 (3.0%)
	PNEUMONIA LOBAR	0 .	1 (0.2%)	1 (0.1%)
	RESPIRATORY DISORDER	8 (3.3%)	21 (4.4%)	29 (4.0%)
	RESPIRATORY INSUFFICIENCY	0 .	3 (0.6%)	3 (0.4%)
	RHINITIS	17 (7.0%)	31 (6.5%)	48 (6.6%)
	SINUSITIS	14 (5.8%)	14 (2.9%)	28 (3.9%)
	SPUTUM INCREASED	0 .	5 (1.0%)	5 (0.7%)
	TRACHEITIS	1 (0.4%)	3 (0.6%)	4 (0.6%)
SKIN AND APPENDAGES	TOTAL	21 (8.6%)	38 (7.9%)	59 (8.2%)
	ALOPECIA	0 .	1 (0.2%)	1 (0.1%)
	BULLOUS ERUPTION	0 .	1 (0.2%)	1 (0.1%)
	DERMATITIS	2 (0.8%)	6 (1.3%)	8 (1.1%)
	DERMATITIS FUNGAL	1 (0.4%)	1 (0.2%)	2 (0.3%)
	DERMATITIS LICHENOID	0 .	2 (0.4%)	2 (0.3%)
	ECZEMA	3 (1.2%)	4 (0.8%)	7 (1.0%)
	FOLLICULITIS	0 .	1 (0.2%)	1 (0.1%)
	FURUNCULOSIS	1 (0.4%)	0 .	1 (0.1%)
	HYPERKERATOSIS	1 (0.4%)	0 .	1 (0.1%)
	PHOTOSENSITIVITY	1 (0.4%)	0 .	1 (0.1%)
	ALLERGIC REACT			
	PRURITUS	2 (0.8%)	11 (2.3%)	13 (1.8%)
	PSORIASIS	0 .	1 (0.2%)	1 (0.1%)
	RASH	3 (1.2%)	5 (1.0%)	8 (1.1%)
	RASH ERYTHEMATOUS	0 .	1 (0.2%)	1 (0.1%)

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TABLE 15.7

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES THAT REQUIRED CORRECTIVE THERAPY BY BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
SKIN AND APPENDAGES	RASH MACULO-PAPULAR	0	3 (0.6%)	3 (0.4%)
	RASH PUSTULAR	0	1 (0.2%)	1 (0.1%)
	ROSACEA	1 (0.4%)	0	1 (0.1%)
	SKIN DISORDER	4 (1.6%)	5 (1.0%)	9 (1.2%)
	SKIN DRY	3 (1.2%)	2 (0.4%)	5 (0.7%)
	SKIN HYPERTROPHY	2 (0.8%)	0	2 (0.3%)
	SKIN ULCERATION	0	3 (0.6%)	3 (0.4%)
	URTICARIA	1 (0.4%)	6 (1.3%)	7 (1.0%)
	VERRUCA	1 (0.4%)	0	1 (0.1%)
URINARY SYSTEM	TOTAL	22 (9.1%)	41 (8.5%)	63 (8.7%)
	ALBUMINURIA	1 (0.4%)	1 (0.2%)	2 (0.3%)
	CYSTITIS	1 (0.4%)	5 (1.0%)	6 (0.8%)
	DYSURIA	5 (2.1%)	2 (0.4%)	7 (1.0%)
	HEMATURIA	5 (2.1%)	4 (0.8%)	9 (1.2%)
	MICTURITION DISORDER	1 (0.4%)	1 (0.2%)	2 (0.3%)
	MICTURITION FREQUENCY	2 (0.8%)	3 (0.6%)	5 (0.7%)
	NOCTURIA	0	1 (0.2%)	1 (0.1%)
	PYELONEPHRITIS	0	2 (0.4%)	2 (0.3%)
	PYURIA	2 (0.8%)	4 (0.8%)	6 (0.8%)
	RENAL CALCULUS	1 (0.4%)	0	1 (0.1%)
	RENAL FAILURE ACUTE	0	1 (0.2%)	1 (0.1%)
	RENAL FUNCTION ABNORMAL	2 (0.8%)	0	2 (0.3%)
	RENAL PAIN	0	1 (0.2%)	1 (0.1%)
	URINARY INCONTINENCE	0	2 (0.4%)	2 (0.3%)
	URINARY RETENTION	1 (0.4%)	4 (0.8%)	5 (0.7%)
	URINARY TRACT INFECTION	9 (3.7%)	21 (4.4%)	30 (4.1%)
VASCULAR EXTRACARDIAC	TOTAL	9 (3.7%)	18 (3.8%)	27 (3.7%)
	ARTERIOSCLEROSIS	0	1 (0.2%)	1 (0.1%)
	ARTERITIS	1 (0.4%)	0	1 (0.1%)
	CEREBROVASCULAR DISORDER	0	3 (0.6%)	3 (0.4%)
	CLAUDICATION INTERMITTENT	2 (0.8%)	1 (0.2%)	3 (0.4%)
	CRAMPS LEGS	1 (0.4%)	2 (0.4%)	3 (0.4%)
	HEMORRHAGE NOS	1 (0.4%)	0	1 (0.1%)
	PERIPHERAL ISCHEMIA	2 (0.8%)	1 (0.2%)	3 (0.4%)

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INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES THAT REQUIRED CORRECTIVE THERAPY BY BODY SYSTEM, PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
VASCULAR EXTRACARDIAC	PHLEBITIS	0 .	1 (0.2%)	1 (0.1%)
	PHLEBITIS SUPERFICIAL	0 .	1 (0.2%)	1 (0.1%)
	THROMBOPHLEBITIS DEEP	1 (0.4%)	0 .	1 (0.1%)
	THROMBOPHLEBITIS LEG	0 .	1 (0.2%)	1 (0.1%)
	THROMBOSIS ARTERIAL LEG	0 .	1 (0.2%)	1 (0.1%)
	THROMBOSIS RETINAL ARTERY	0 .	1 (0.2%)	1 (0.1%)
	VASCULAR DISORDER	1 (0.4%)	3 (0.6%)	4 (0.6%)
	VEIN DISORDER	1 (0.4%)	1 (0.2%)	2 (0.3%)
	VEIN VARICOSE	0 .	3 (0.6%)	3 (0.4%)
VISION	TOTAL	12 (4.9%)	16 (3.3%)	28 (3.9%)
	BLEPHARITIS	2 (0.8%)	1 (0.2%)	3 (0.4%)
	CATARACT	4 (1.6%)	4 (0.8%)	8 (1.1%)
	CONJUNCTIVITIS	7 (2.9%)	6 (1.3%)	13 (1.8%)
	CORNEAL ULCERATION	0 .	1 (0.2%)	1 (0.1%)
	EYE ABNORMALITY	2 (0.8%)	1 (0.2%)	3 (0.4%)
	GLAUCOMA	0 .	1 (0.2%)	1 (0.1%)
	RETINAL DETACHMENT	1 (0.4%)	0 .	1 (0.1%)
	UVEITIS	0 .	1 (0.2%)	1 (0.1%)
	VISION ABNORMAL	1 (0.4%)	1 (0.2%)	2 (0.3%)
	VISUAL FIELD DEFECT	0 .	1 (0.2%)	1 (0.1%)
	XEROPHTHALMIA	2 (0.8%)	0 .	2 (0.3%)
WHITE CELL AND RETICULOENDOTHELIAL SYSTE	TOTAL	6 (2.5%)	3 (0.6%)	9 (1.2%)
	LEUKOCYTOSIS	1 (0.4%)	2 (0.4%)	3 (0.4%)
	LYMPHADENOPATHY	3 (1.2%)	1 (0.2%)	4 (0.6%)
	LYMPHADENOPATHY CERVICAL	0 .	1 (0.2%)	1 (0.1%)
	LYMPHANGITIS	1 (0.4%)	0 .	1 (0.1%)
	LYMPHEDEMA	1 (0.4%)	0 .	1 (0.1%)

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TABLE 15.8A

INCIDENCE OF ON-THERAPY SERIOUS ADVERSE EXPERIENCES BY BODY SYSTEM, PREFERRED TERM AND
PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
TOTAL	TOTAL	63 (25.9%)	116 (24.2%)	179 (24.8%)
APPLICATION SITE	TOTAL	0 .	1 (0.2%)	1 (0.1%)
	OTITIS EXTERNA	0 .	1 (0.2%)	1 (0.1%)
BODY AS A WHOLE GENERAL	TOTAL	5 (2.1%)	24 (5.0%)	29 (4.0%)
	ASTHENIA	0 .	2 (0.4%)	2 (0.3%)
	CELLULITIS	1 (0.4%)	1 (0.2%)	2 (0.3%)
	CHEST PAIN	2 (0.8%)	5 (1.0%)	7 (1.0%)
	INJURY	2 (0.8%)	14 (2.9%)	16 (2.2%)
	MALAISE	0 .	1 (0.2%)	1 (0.1%)
	PAIN	0 .	1 (0.2%)	1 (0.1%)
	THERAPEUTIC RESPONSE INCREASED	0 .	2 (0.4%)	2 (0.3%)
CARDIOVASCULAR GENERAL	TOTAL	3 (1.2%)	5 (1.0%)	8 (1.1%)
	ANEURYSM	1 (0.4%)	2 (0.4%)	3 (0.4%)
	CARDIAC FAILURE	1 (0.4%)	1 (0.2%)	2 (0.3%)
	HYPERTENSION PULMONARY	0 .	1 (0.2%)	1 (0.1%)
	SYNCOPE	1 (0.4%)	1 (0.2%)	2 (0.3%)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	TOTAL	0 .	7 (1.5%)	7 (1.0%)
	COMA	0 .	1 (0.2%)	1 (0.1%)
	CONVULSIONS	0 .	2 (0.4%)	2 (0.3%)
	DIZZINESS	0 .	1 (0.2%)	1 (0.1%)
	NEURALGIA	0 .	2 (0.4%)	2 (0.3%)
	VERTIGO	0 .	1 (0.2%)	1 (0.1%)
COLLAGEN	TOTAL	0 .	1 (0.2%)	1 (0.1%)
	ARTHRITIS RHEUMATOID AGGRAVATED	0 .	1 (0.2%)	1 (0.1%)
ENDOCRINE	TOTAL	1 (0.4%)	2 (0.4%)	3 (0.4%)
	GOITRE	0 .	1 (0.2%)	1 (0.1%)
	HYPERTHYROIDISM	1 (0.4%)	1 (0.2%)	2 (0.3%)

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TABLE 15.8A

INCIDENCE OF ON-THERAPY SERIOUS ADVERSE EXPERIENCES BY BODY SYSTEM, PREFERRED TERM AND
PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
GASTROINTESTINAL SYSTEM	TOTAL	6 (2.5%)	15 (3.1%)	21 (2.9%)
	ABDOMINAL PAIN	2 (0.8%)	0 .	2 (0.3%)
	DIARRHEA	1 (0.4%)	0 .	1 (0.1%)
	DIVERTICULITIS	0 .	2 (0.4%)	2 (0.3%)
	DYSPHAGIA	0 .	1 (0.2%)	1 (0.1%)
	GASTROENTERITIS	0 .	1 (0.2%)	1 (0.1%)
	GASTROINTESTINAL DISORDER NOS	1 (0.4%)	2 (0.4%)	3 (0.4%)
	GI HEMORRHAGE	2 (0.8%)	1 (0.2%)	3 (0.4%)
	HEMATEMESIS	0 .	1 (0.2%)	1 (0.1%)
	HEMORRHOIDS	0 .	2 (0.4%)	2 (0.3%)
	INTESTINAL OBSTRUCTION	1 (0.4%)	3 (0.6%)	4 (0.6%)
	NAUSEA	0 .	1 (0.2%)	1 (0.1%)
	PANCREATITIS	0 .	1 (0.2%)	1 (0.1%)
	PERITONITIS	0 .	1 (0.2%)	1 (0.1%)
	VOMITING	1 (0.4%)	0 .	1 (0.1%)
HEART RATE AND RHYTHM	TOTAL	2 (0.8%)	5 (1.0%)	7 (1.0%)
	ARRHYTHMIA ATRIAL	1 (0.4%)	1 (0.2%)	2 (0.3%)
	CARDIAC ARREST	0 .	1 (0.2%)	1 (0.1%)
	FIBRILLATION ATRIAL	1 (0.4%)	2 (0.4%)	3 (0.4%)
	PALPITATION	0 .	1 (0.2%)	1 (0.1%)
LIVER AND BILIARY SYSTEM	TOTAL	1 (0.4%)	3 (0.6%)	4 (0.6%)
	CHOLECYSTITIS	0 .	2 (0.4%)	2 (0.3%)
	CHOLELITHIASIS	0 .	1 (0.2%)	1 (0.1%)
	HEPATIC CIRRHOSIS	1 (0.4%)	0 .	1 (0.1%)
METABOLIC AND NUTRITIONAL	TOTAL	1 (0.4%)	0 .	1 (0.1%)
	WEIGHT DECREASE	1 (0.4%)	0 .	1 (0.1%)
MUSCULOSKELETAL SYSTEM	TOTAL	3 (1.2%)	4 (0.8%)	7 (1.0%)
	ARTHROPATHY	0 .	1 (0.2%)	1 (0.1%)
	ARTHROSIS	1 (0.4%)	0 .	1 (0.1%)
	BONE DISORDER	0 .	1 (0.2%)	1 (0.1%)
	BURSITIS	0 .	1 (0.2%)	1 (0.1%)

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TABLE 15.8A

INCIDENCE OF ON-THERAPY SERIOUS ADVERSE EXPERIENCES BY BODY SYSTEM, PREFERRED TERM AND
PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
MUSCULOSKELETAL SYSTEM	MYALGIA	0 .	1 (0.2%)	1 (0.1%)
	OSTEONECROSIS	1 (0.4%)	0 .	1 (0.1%)
	TENDON DISORDER	1 (0.4%)	0 .	1 (0.1%)
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	TOTAL	4 (1.6%)	7 (1.5%)	11 (1.5%)
	ANGINA PECTORIS	3 (1.2%)	4 (0.8%)	7 (1.0%)
	ANGINA PECTORIS AGGRAVATED	0 .	1 (0.2%)	1 (0.1%)
	MYOCARDIAL INFARCTION	1 (0.4%)	1 (0.2%)	2 (0.3%)
	MYOCARDIAL ISCHEMIA	0 .	1 (0.2%)	1 (0.1%)
NEOPLASM	TOTAL	14 (5.8%)	16 (3.3%)	30 (4.1%)
	ADENOCARCINOMA NOS	1 (0.4%)	1 (0.2%)	2 (0.3%)
	BASAL CELL CARCINOMA	1 (0.4%)	0 .	1 (0.1%)
	BLADDER CARCINOMA	2 (0.8%)	0 .	2 (0.3%)
	CARCINOMA	2 (0.8%)	2 (0.4%)	4 (0.6%)
	COLON CARCINOMA	1 (0.4%)	0 .	1 (0.1%)
	GASTRIC CARCINOMA	1 (0.4%)	0 .	1 (0.1%)
	GI NEOPLASM MALIGNANT	0 .	1 (0.2%)	1 (0.1%)
	LYMPHOMA MALIGNANT	1 (0.4%)	0 .	1 (0.1%)
	NEOPLASM MALIGNANT	1 (0.4%)	0 .	1 (0.1%)
	NEOPLASM NOS	3 (1.2%)	5 (1.0%)	8 (1.1%)
	PULMONARY CARCINOMA	1 (0.4%)	7 (1.5%)	8 (1.1%)
PSYCHIATRIC	TOTAL	0 .	2 (0.4%)	2 (0.3%)
	DEPRESSION	0 .	1 (0.2%)	1 (0.1%)
	SUICIDE ATTEMPT	0 .	1 (0.2%)	1 (0.1%)
REPRODUCTIVE FEMALE	TOTAL	1 (0.4%)	0 .	1 (0.1%)
	PELVIC INFLAMMATION	1 (0.4%)	0 .	1 (0.1%)
RESISTANCE MECHANISM	TOTAL	2 (0.8%)	6 (1.3%)	8 (1.1%)
	HERPES ZOSTER	1 (0.4%)	3 (0.6%)	4 (0.6%)
	INFECTION	0 .	1 (0.2%)	1 (0.1%)
	SEPSIS	1 (0.4%)	2 (0.4%)	3 (0.4%)
RESPIRATORY SYSTEM	TOTAL	26 (10.7%)	53 (11.0%)	79 (10.9%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM/PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AN ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 15.8A

INCIDENCE OF ON-THERAPY SERIOUS ADVERSE EXPERIENCES BY BODY SYSTEM, PREFERRED TERM AND
PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
RESPIRATORY SYSTEM	BRONCHITIS	0	2 (0.4%)	2 (0.3%)
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	20 (8.2%)	35 (7.3%)	55 (7.6%)
	EPISTAXIS	0	1 (0.2%)	1 (0.1%)
	LARYNGITIS	1 (0.4%)	0	1 (0.1%)
	PLEURAL EFFUSION	0	1 (0.2%)	1 (0.1%)
	PLEURISY	0	1 (0.2%)	1 (0.1%)
	PNEUMONIA	7 (2.9%)	10 (2.1%)	17 (2.4%)
	PNEUMONIA LOBAR	0	1 (0.2%)	1 (0.1%)
	RESPIRATORY DISORDER	1 (0.4%)	3 (0.6%)	4 (0.6%)
	RESPIRATORY INSUFFICIENCY	0	3 (0.6%)	3 (0.4%)
SKIN AND APPENDAGES	TOTAL	1 (0.4%)	1 (0.2%)	2 (0.3%)
	DERMATITIS	0	1 (0.2%)	1 (0.1%)
	SKIN DISORDER	1 (0.4%)	0	1 (0.1%)
URINARY SYSTEM	TOTAL	2 (0.8%)	8 (1.7%)	10 (1.4%)
	HEMATURIA	1 (0.4%)	0	1 (0.1%)
	PYELONEPHRITIS	0	2 (0.4%)	2 (0.3%)
	RENAL FAILURE ACUTE	0	2 (0.4%)	2 (0.3%)
	RENAL PAIN	0	1 (0.2%)	1 (0.1%)
	URINARY RETENTION	1 (0.4%)	2 (0.4%)	3 (0.4%)
	URINARY TRACT INFECTION	1 (0.4%)	1 (0.2%)	2 (0.3%)
VASCULAR EXTRACARDIAC	TOTAL	1 (0.4%)	3 (0.6%)	4 (0.6%)
	CEREBROVASCULAR DISORDER	0	2 (0.4%)	2 (0.3%)
	THROMBOPHLEBITIS DEEP	1 (0.4%)	0	1 (0.1%)
	THROMBOSIS RETINAL ARTERY	0	1 (0.2%)	1 (0.1%)
VISION	TOTAL	4 (1.6%)	2 (0.4%)	6 (0.8%)
	CATARACT	3 (1.2%)	2 (0.4%)	5 (0.7%)
	RETINAL DETACHMENT	1 (0.4%)	0	1 (0.1%)
WHITE CELL AND RETICULOENDOTHELIAL SYSTE	TOTAL	1 (0.4%)	0	1 (0.1%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM/PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AN ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 15.8A

INCIDENCE OF ON-THERAPY SERIOUS ADVERSE EXPERIENCES BY BODY SYSTEM, PREFERRED TERM AND
PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PRIOR TREATMENT		Total (N=723)
		PLACEBO (N=243)	SB 207499 (N=480)	
WHITE CELL AND RETICULOENDOTHELIAL SYSTE	LEUKOCYTOSIS	1 (0.4%)	0 .	1 (0.1%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM/PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AN ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 15.8B

INCIDENCE OF POST-THERAPY SERIOUS ADVERSE EXPERIENCES BY BODY SYSTEM, PREFERRED TERM AND
PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
TOTAL	TOTAL	12 (4.9%)	22 (4.6%)	34 (4.7%)
BODY AS A WHOLE GENERAL	TOTAL	0 .	2 (0.4%)	2 (0.3%)
	CONDITION AGGRAVATED	0 .	1 (0.2%)	1 (0.1%)
	SUDDEN DEATH	0 .	1 (0.2%)	1 (0.1%)
CARDIOVASCULAR GENERAL	TOTAL	2 (0.8%)	1 (0.2%)	3 (0.4%)
	ANEURYSM	1 (0.4%)	0 .	1 (0.1%)
	CARDIAC FAILURE LEFT	0 .	1 (0.2%)	1 (0.1%)
	CIRCULATORY FAILURE	1 (0.4%)	0 .	1 (0.1%)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	TOTAL	1 (0.4%)	1 (0.2%)	2 (0.3%)
	DIZZINESS	0 .	1 (0.2%)	1 (0.1%)
	ENCEPHALOPATHY	1 (0.4%)	0 .	1 (0.1%)
GASTROINTESTINAL SYSTEM	TOTAL	0 .	3 (0.6%)	3 (0.4%)
	DIARRHEA	0 .	1 (0.2%)	1 (0.1%)
	DIVERTICULITIS	0 .	1 (0.2%)	1 (0.1%)
	PERITONITIS	0 .	1 (0.2%)	1 (0.1%)
HEART RATE AND RHYTHM	TOTAL	1 (0.4%)	5 (1.0%)	6 (0.8%)
	ARRHYTHMIA ATRIAL	0 .	1 (0.2%)	1 (0.1%)
	ATRIOVENTRICULAR	0 .	1 (0.2%)	1 (0.1%)
	BLOCK COMPLETE			
	CARDIAC ARREST	1 (0.4%)	3 (0.6%)	4 (0.6%)
MUSCULOSKELETAL SYSTEM	TOTAL	1 (0.4%)	0 .	1 (0.1%)
	ARTHROPATHY	1 (0.4%)	0 .	1 (0.1%)
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	TOTAL	2 (0.8%)	1 (0.2%)	3 (0.4%)
	ANGINA PECTORIS	1 (0.4%)	0 .	1 (0.1%)
	AGGRAVATED			

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM/PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AN ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 15.8B

INCIDENCE OF POST-THERAPY SERIOUS ADVERSE EXPERIENCES BY BODY SYSTEM, PREFERRED TERM AND
PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	CORONARY ARTERY DISORDER	0 .	1 (0.2%)	1 (0.1%)
	MYOCARDIAL INFARCTION	1 (0.4%)	0 .	1 (0.1%)
NEOPLASM	TOTAL	2 (0.8%)	4 (0.8%)	6 (0.8%)
	ADENOCARCINOMA NOS	1 (0.4%)	0 .	1 (0.1%)
	CARCINOMA	1 (0.4%)	0 .	1 (0.1%)
	ESOPHAGEAL CARCINOMA	0 .	1 (0.2%)	1 (0.1%)
	NEOPLASM MALIGNANT	0 .	1 (0.2%)	1 (0.1%)
	PULMONARY CARCINOMA	0 .	2 (0.4%)	2 (0.3%)
REPRODUCTIVE MALE	TOTAL	1 (0.4%)	0 .	1 (0.1%)
	ORCHITIS	1 (0.4%)	0 .	1 (0.1%)
RESISTANCE MECHANISM	TOTAL	1 (0.4%)	2 (0.4%)	3 (0.4%)
	INFECTION	0 .	1 (0.2%)	1 (0.1%)
	INFECTION TBC	0 .	1 (0.2%)	1 (0.1%)
	SEPSIS	1 (0.4%)	0 .	1 (0.1%)
RESPIRATORY SYSTEM	TOTAL	5 (2.1%)	8 (1.7%)	13 (1.8%)
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	3 (1.2%)	6 (1.3%)	9 (1.2%)
	PNEUMONIA	1 (0.4%)	2 (0.4%)	3 (0.4%)
	PNEUMOTHORAX	2 (0.8%)	0 .	2 (0.3%)
	RESPIRATORY INSUFFICIENCY	1 (0.4%)	0 .	1 (0.1%)
URINARY SYSTEM	TOTAL	0 .	1 (0.2%)	1 (0.1%)
	RENAL FAILURE ACUTE	0 .	1 (0.2%)	1 (0.1%)
VASCULAR EXTRACARDIAC	TOTAL	0 .	1 (0.2%)	1 (0.1%)
	THROMBOSIS	0 .	1 (0.2%)	1 (0.1%)
	THROMBOSIS MESENTERIC VESSEL	0 .	1 (0.2%)	1 (0.1%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM/PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AN ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 15.9A

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES LEADING TO PATIENT WITHDRAWAL BY PREFERRED TERM,
DESCENDING FREQUENCY OF OCCURRENCE AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
TOTAL	45 (18.5%)	57 (11.9%)	102 (14.1%)
ABDOMINAL PAIN	13 (5.3%)	11 (2.3%)	24 (3.3%)
NAUSEA	8 (3.3%)	3 (0.6%)	11 (1.5%)
DIARRHEA	6 (2.5%)	4 (0.8%)	10 (1.4%)
CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	4 (1.6%)	5 (1.0%)	9 (1.2%)
PULMONARY CARCINOMA	1 (0.4%)	7 (1.5%)	8 (1.1%)
VOMITING	6 (2.5%)	2 (0.4%)	8 (1.1%)
CARCINOMA	1 (0.4%)	2 (0.4%)	3 (0.4%)
HEADACHE	2 (0.8%)	1 (0.2%)	3 (0.4%)
PNEUMONIA	1 (0.4%)	2 (0.4%)	3 (0.4%)
ANEURYSM	1 (0.4%)	1 (0.2%)	2 (0.3%)
ANGINA PECTORIS	1 (0.4%)	1 (0.2%)	2 (0.3%)
ASTHENIA	1 (0.4%)	1 (0.2%)	2 (0.3%)
DERMATITIS	0 .	2 (0.4%)	2 (0.3%)
DIZZINESS	1 (0.4%)	1 (0.2%)	2 (0.3%)
DYSPEPSIA	2 (0.8%)	0 .	2 (0.3%)
FIBRILLATION ATRIAL	1 (0.4%)	1 (0.2%)	2 (0.3%)
GASTRITIS	0 .	2 (0.4%)	2 (0.3%)
GI HEMORRHAGE	1 (0.4%)	1 (0.2%)	2 (0.3%)
GOITRE	1 (0.4%)	1 (0.2%)	2 (0.3%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AN ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091
5. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO THE TOTAL GROUP

SB 207499

TABLE 15.9A

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES LEADING TO PATIENT WITHDRAWAL BY PREFERRED TERM,
DESCENDING FREQUENCY OF OCCURRENCE AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
ANEMIA	0 .	1 (0.2%)	1 (0.1%)
ANOREXIA	1 (0.4%)	0 .	1 (0.1%)
ANXIETY	1 (0.4%)	0 .	1 (0.1%)
BILIRUBINEMIA	1 (0.4%)	0 .	1 (0.1%)
CARDIAC ARREST	0 .	1 (0.2%)	1 (0.1%)
CARDIAC FAILURE	1 (0.4%)	0 .	1 (0.1%)
CHEST PAIN	0 .	1 (0.2%)	1 (0.1%)
COLON CARCINOMA	1 (0.4%)	0 .	1 (0.1%)
FATIGUE	1 (0.4%)	0 .	1 (0.1%)
GAMMA-GT INCREASED	1 (0.4%)	0 .	1 (0.1%)
GASTRIC CARCINOMA	1 (0.4%)	0 .	1 (0.1%)
GASTROINTESTINAL DISORDER NOS	0 .	1 (0.2%)	1 (0.1%)
GI NEOPLASM MALIGNANT	0 .	1 (0.2%)	1 (0.1%)
HEMATURIA	0 .	1 (0.2%)	1 (0.1%)
HEPATIC ENZYMES INCREASED	1 (0.4%)	0 .	1 (0.1%)
HEPATIC FUNCTION ABNORMAL	0 .	1 (0.2%)	1 (0.1%)
HYPERTENSION PULMONARY	0 .	1 (0.2%)	1 (0.1%)
INJURY	0 .	1 (0.2%)	1 (0.1%)
LYMPHOMA MALIGNANT	1 (0.4%)	0 .	1 (0.1%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AN ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091
5. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO THE TOTAL GROUP

TABLE 15.9A

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES LEADING TO PATIENT WITHDRAWAL BY PREFERRED TERM,
DESCENDING FREQUENCY OF OCCURRENCE AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
MYOCARDIAL INFARCTION	0 .	1 (0.2%)	1 (0.1%)
NEOPLASM MALIGNANT	1 (0.4%)	0 .	1 (0.1%)
NEOPLASM NOS	0 .	1 (0.2%)	1 (0.1%)
NERVOUSNESS	1 (0.4%)	0 .	1 (0.1%)
PARKINSONISM AGGRAVATED	0 .	1 (0.2%)	1 (0.1%)
PERITONITIS	0 .	1 (0.2%)	1 (0.1%)
PRURITUS	1 (0.4%)	0 .	1 (0.1%)
RENAL FAILURE ACUTE	0 .	1 (0.2%)	1 (0.1%)
RESPIRATORY DISORDER	0 .	1 (0.2%)	1 (0.1%)
SUICIDE ATTEMPT	0 .	1 (0.2%)	1 (0.1%)
TACHYCARDIA	1 (0.4%)	0 .	1 (0.1%)
TASTE PERVERSION	0 .	1 (0.2%)	1 (0.1%)
WEIGHT DECREASE	1 (0.4%)	0 .	1 (0.1%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AN ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091
5. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO THE TOTAL GROUP

TABLE 15.9B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES LEADING TO PATIENT WITHDRAWAL BY BODY SYSTEM,
PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
TOTAL	TOTAL	45 (18.5%)	57 (11.9%)	102 (14.1%)
BODY AS A WHOLE GENERAL	TOTAL	2 (0.8%)	3 (0.6%)	5 (0.7%)
	ASTHENIA	1 (0.4%)	1 (0.2%)	2 (0.3%)
	CHEST PAIN	0 .	1 (0.2%)	1 (0.1%)
	FATIGUE	1 (0.4%)	0 .	1 (0.1%)
	INJURY	0 .	1 (0.2%)	1 (0.1%)
CARDIOVASCULAR GENERAL	TOTAL	2 (0.8%)	2 (0.4%)	4 (0.6%)
	ANEURYSM	1 (0.4%)	1 (0.2%)	2 (0.3%)
	CARDIAC FAILURE	1 (0.4%)	0 .	1 (0.1%)
	HYPERTENSION PULMONARY	0 .	1 (0.2%)	1 (0.1%)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	TOTAL	3 (1.2%)	3 (0.6%)	6 (0.8%)
	DIZZINESS	1 (0.4%)	1 (0.2%)	2 (0.3%)
	HEADACHE	2 (0.8%)	1 (0.2%)	3 (0.4%)
	PARKINSONISM AGGRAVATED	0 .	1 (0.2%)	1 (0.1%)
ENDOCRINE	TOTAL	1 (0.4%)	1 (0.2%)	2 (0.3%)
	GOITRE	1 (0.4%)	1 (0.2%)	2 (0.3%)
GASTROINTESTINAL SYSTEM	TOTAL	22 (9.1%)	20 (4.2%)	42 (5.8%)
	ABDOMINAL PAIN	13 (5.3%)	11 (2.3%)	24 (3.3%)
	ANOREXIA	1 (0.4%)	0 .	1 (0.1%)
	DIARRHEA	6 (2.5%)	4 (0.8%)	10 (1.4%)
	DYSPEPSIA	2 (0.8%)	0 .	2 (0.3%)
	GASTRITIS	0 .	2 (0.4%)	2 (0.3%)
	GASTROINTESTINAL DISORDER NOS	0 .	1 (0.2%)	1 (0.1%)
	GI HEMORRHAGE	1 (0.4%)	1 (0.2%)	2 (0.3%)
	NAUSEA	8 (3.3%)	3 (0.6%)	11 (1.5%)
	PERITONITIS	0 .	1 (0.2%)	1 (0.1%)
	VOMITING	6 (2.5%)	2 (0.4%)	8 (1.1%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM/PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AN ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 15.9B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES LEADING TO PATIENT WITHDRAWAL BY BODY SYSTEM,
PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
HEART RATE AND RHYTHM	TOTAL	2 (0.8%)	2 (0.4%)	4 (0.6%)
	CARDIAC ARREST	0 .	1 (0.2%)	1 (0.1%)
	FIBRILLATION ATRIAL	1 (0.4%)	1 (0.2%)	2 (0.3%)
	TACHYCARDIA	1 (0.4%)	0 .	1 (0.1%)
LIVER AND BILIARY SYSTEM	TOTAL	2 (0.8%)	1 (0.2%)	3 (0.4%)
	BILIRUBINEMIA	1 (0.4%)	0 .	1 (0.1%)
	GAMMA-GT INCREASED	1 (0.4%)	0 .	1 (0.1%)
	HEPATIC ENZYMES INCREASED	1 (0.4%)	0 .	1 (0.1%)
	HEPATIC FUNCTION ABNORMAL	0 .	1 (0.2%)	1 (0.1%)
METABOLIC AND NUTRITIONAL	TOTAL	1 (0.4%)	0 .	1 (0.1%)
	WEIGHT DECREASE	1 (0.4%)	0 .	1 (0.1%)
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	TOTAL	1 (0.4%)	2 (0.4%)	3 (0.4%)
	ANGINA PECTORIS	1 (0.4%)	1 (0.2%)	2 (0.3%)
	MYOCARDIAL INFARCTION	0 .	1 (0.2%)	1 (0.1%)
NEOPLASM	TOTAL	6 (2.5%)	11 (2.3%)	17 (2.4%)
	CARCINOMA	1 (0.4%)	2 (0.4%)	3 (0.4%)
	COLON CARCINOMA	1 (0.4%)	0 .	1 (0.1%)
	GASTRIC CARCINOMA	1 (0.4%)	0 .	1 (0.1%)
	GI NEOPLASM MALIGNANT	0 .	1 (0.2%)	1 (0.1%)
	LYMPHOMA MALIGNANT	1 (0.4%)	0 .	1 (0.1%)
	NEOPLASM MALIGNANT	1 (0.4%)	0 .	1 (0.1%)
	NEOPLASM NOS	0 .	1 (0.2%)	1 (0.1%)
	PULMONARY CARCINOMA	1 (0.4%)	7 (1.5%)	8 (1.1%)
PSYCHIATRIC	TOTAL	2 (0.8%)	1 (0.2%)	3 (0.4%)
	ANXIETY	1 (0.4%)	0 .	1 (0.1%)
	NERVOUSNESS	1 (0.4%)	0 .	1 (0.1%)
	SUICIDE ATTEMPT	0 .	1 (0.2%)	1 (0.1%)
RED BLOOD CELL	TOTAL	0 .	1 (0.2%)	1 (0.1%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM/PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AN ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 15.9B

INCIDENCE OF ON-THERAPY ADVERSE EXPERIENCES LEADING TO PATIENT WITHDRAWAL BY BODY SYSTEM,
PREFERRED TERM AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
RED BLOOD CELL	ANEMIA	0 .	1 (0.2%)	1 (0.1%)
RESPIRATORY SYSTEM	TOTAL	5 (2.1%)	8 (1.7%)	13 (1.8%)
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	4 (1.6%)	5 (1.0%)	9 (1.2%)
	PNEUMONIA	1 (0.4%)	2 (0.4%)	3 (0.4%)
	RESPIRATORY DISORDER	0 .	1 (0.2%)	1 (0.1%)
SKIN AND APPENDAGES	TOTAL	1 (0.4%)	2 (0.4%)	3 (0.4%)
	DERMATITIS	0 .	2 (0.4%)	2 (0.3%)
	PRURITUS	1 (0.4%)	0 .	1 (0.1%)
SPECIAL SENSES	TOTAL	0 .	1 (0.2%)	1 (0.1%)
OTHER	TASTE PERVERSION	0 .	1 (0.2%)	1 (0.1%)
URINARY SYSTEM	TOTAL	0 .	2 (0.4%)	2 (0.3%)
	HEMATURIA	0 .	1 (0.2%)	1 (0.1%)
	RENAL FAILURE ACUTE	0 .	1 (0.2%)	1 (0.1%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM/PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AN ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 15.10

INCIDENCE OF ALL POST-THERAPY ADVERSE EXPERIENCES BY BODY SYSTEM, PREFERRED TERM AND
PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
TOTAL	TOTAL	22 (9.1%)	39 (8.1%)	61 (8.4%)
BODY AS A WHOLE GENERAL	TOTAL	1 (0.4%)	6 (1.3%)	7 (1.0%)
	CHEST PAIN	0 .	1 (0.2%)	1 (0.1%)
	CONDITION AGGRAVATED	0 .	1 (0.2%)	1 (0.1%)
	EDEMA	1 (0.4%)	0 .	1 (0.1%)
	EDEMA LEGS	0 .	1 (0.2%)	1 (0.1%)
	FEVER	0 .	1 (0.2%)	1 (0.1%)
	INJURY	0 .	1 (0.2%)	1 (0.1%)
	SUDDEN DEATH	0 .	1 (0.2%)	1 (0.1%)
CARDIOVASCULAR GENERAL	TOTAL	4 (1.6%)	1 (0.2%)	5 (0.7%)
	ANEURYSM	1 (0.4%)	0 .	1 (0.1%)
	CARDIAC FAILURE LEFT	0 .	1 (0.2%)	1 (0.1%)
	CIRCULATORY FAILURE	1 (0.4%)	0 .	1 (0.1%)
	ECG ABNORMAL	1 (0.4%)	0 .	1 (0.1%)
	SYNCOPE	1 (0.4%)	0 .	1 (0.1%)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	TOTAL	1 (0.4%)	1 (0.2%)	2 (0.3%)
	DIZZINESS	0 .	1 (0.2%)	1 (0.1%)
	ENCEPHALOPATHY	1 (0.4%)	0 .	1 (0.1%)
GASTROINTESTINAL SYSTEM	TOTAL	4 (1.6%)	6 (1.3%)	10 (1.4%)
	ABDOMINAL PAIN	0 .	1 (0.2%)	1 (0.1%)
	ANOREXIA	1 (0.4%)	0 .	1 (0.1%)
	CONSTIPATION	2 (0.8%)	0 .	2 (0.3%)
	DIARRHEA	0 .	2 (0.4%)	2 (0.3%)
	DIVERTICULITIS	0 .	2 (0.4%)	2 (0.3%)
	HEMORRHAGE RECTUM	1 (0.4%)	0 .	1 (0.1%)
	PERITONITIS	0 .	1 (0.2%)	1 (0.1%)
HEARING AND VESTIBULAR	TOTAL	0 .	1 (0.2%)	1 (0.1%)
	HEARING DECREASED	0 .	1 (0.2%)	1 (0.1%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM/PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AN ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 15.10

INCIDENCE OF ALL POST-THERAPY ADVERSE EXPERIENCES BY BODY SYSTEM, PREFERRED TERM AND
PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
HEART RATE AND RHYTHM	TOTAL	1 (0.4%)	5 (1.0%)	6 (0.8%)
	ARRHYTHMIA ATRIAL	0 .	1 (0.2%)	1 (0.1%)
	ATRIOVENTRICULAR BLOCK COMPLETE	0 .	1 (0.2%)	1 (0.1%)
	CARDIAC ARREST	1 (0.4%)	3 (0.6%)	4 (0.6%)
METABOLIC AND NUTRITIONAL	TOTAL	2 (0.8%)	2 (0.4%)	4 (0.6%)
	ACIDOSIS	1 (0.4%)	0 .	1 (0.1%)
	HYPERCHOLESTEROLEMIA	0 .	1 (0.2%)	1 (0.1%)
	NPN INCREASED	0 .	1 (0.2%)	1 (0.1%)
MUSCULOSKELETAL SYSTEM	WEIGHT DECREASE	1 (0.4%)	0 .	1 (0.1%)
	TOTAL	1 (0.4%)	1 (0.2%)	2 (0.3%)
	ARTHROPATHY	1 (0.4%)	0 .	1 (0.1%)
	MYALGIA	0 .	1 (0.2%)	1 (0.1%)
MYOCARDIAL ENDOCARDIAL PERICARDIAL VALVE	TOTAL	2 (0.8%)	1 (0.2%)	3 (0.4%)
	ANGINA PECTORIS	1 (0.4%)	0 .	1 (0.1%)
	AGGRAVATED CORONARY ARTERY DISORDER	0 .	1 (0.2%)	1 (0.1%)
	MYOCARDIAL INFARCTION	1 (0.4%)	0 .	1 (0.1%)
NEOPLASM	TOTAL	2 (0.8%)	4 (0.8%)	6 (0.8%)
	ADENOCARCINOMA NOS	1 (0.4%)	0 .	1 (0.1%)
	CARCINOMA	1 (0.4%)	0 .	1 (0.1%)
	ESOPHAGEAL CARCINOMA	0 .	1 (0.2%)	1 (0.1%)
	NEOPLASM MALIGNANT	0 .	1 (0.2%)	1 (0.1%)
	PULMONARY CARCINOMA	0 .	2 (0.4%)	2 (0.3%)
PLATELET BLEEDING AND CLOTTING	TOTAL	0 .	1 (0.2%)	1 (0.1%)
	THROMBOCYTHEMIA	0 .	1 (0.2%)	1 (0.1%)
PSYCHIATRIC	TOTAL	2 (0.8%)	0 .	2 (0.3%)
	AGITATION	1 (0.4%)	0 .	1 (0.1%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM/PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AN ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 15.10

INCIDENCE OF ALL POST-THERAPY ADVERSE EXPERIENCES BY BODY SYSTEM, PREFERRED TERM AND
PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
PSYCHIATRIC	ANXIETY	1 (0.4%)	0 .	1 (0.1%)
RED BLOOD CELL	TOTAL	1 (0.4%)	0 .	1 (0.1%)
	ANEMIA	1 (0.4%)	0 .	1 (0.1%)
REPRODUCTIVE MALE	TOTAL	1 (0.4%)	1 (0.2%)	2 (0.3%)
	ORCHITIS	1 (0.4%)	0 .	1 (0.1%)
	PROSTATIC DISORDER	0 .	1 (0.2%)	1 (0.1%)
RESISTANCE MECHANISM	TOTAL	3 (1.2%)	4 (0.8%)	7 (1.0%)
	INFECTION	0 .	2 (0.4%)	2 (0.3%)
	INFECTION BACTERIAL	1 (0.4%)	0 .	1 (0.1%)
	INFECTION TBC	0 .	1 (0.2%)	1 (0.1%)
	INFECTION VIRAL	0 .	1 (0.2%)	1 (0.1%)
	SEPSIS	1 (0.4%)	0 .	1 (0.1%)
	UPPER RESP TRACT INFECTION	1 (0.4%)	0 .	1 (0.1%)
RESPIRATORY SYSTEM	TOTAL	9 (3.7%)	16 (3.3%)	25 (3.5%)
	ASTHMA	0 .	1 (0.2%)	1 (0.1%)
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	6 (2.5%)	12 (2.5%)	18 (2.5%)
	PHARYNGITIS	0 .	1 (0.2%)	1 (0.1%)
	PNEUMONIA	2 (0.8%)	2 (0.4%)	4 (0.6%)
	PNEUMOTHORAX	2 (0.8%)	0 .	2 (0.3%)
	RESPIRATORY INSUFFICIENCY	1 (0.4%)	0 .	1 (0.1%)
	RHINITIS	0 .	1 (0.2%)	1 (0.1%)
URINARY SYSTEM	TOTAL	2 (0.8%)	2 (0.4%)	4 (0.6%)
	CYSTITIS	0 .	1 (0.2%)	1 (0.1%)
	MICTURITION DISORDER	1 (0.4%)	0 .	1 (0.1%)
	RENAL FAILURE ACUTE	1 (0.4%)	1 (0.2%)	2 (0.3%)
VASCULAR EXTRACARDIAC	TOTAL	1 (0.4%)	1 (0.2%)	2 (0.3%)
	SUBARACHNOID HEMORRHAGE	1 (0.4%)	0 .	1 (0.1%)
	THROMBOSIS	0 .	1 (0.2%)	1 (0.1%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM/PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AN ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 15.10

INCIDENCE OF ALL POST-THERAPY ADVERSE EXPERIENCES BY BODY SYSTEM, PREFERRED TERM AND
PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO BODY SYSTEM	WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
VASCULAR EXTRACARDIAC	THROMBOSIS MESENTERIC VESSEL	0 .	1 (0.2%)	1 (0.1%)
WHITE CELL AND RETICULOENDOTHELIAL SYSTE	TOTAL	0 .	1 (0.2%)	1 (0.1%)
	LEUKOCYTOSIS	0 .	1 (0.2%)	1 (0.1%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER BODY SYSTEM/PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AN ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091

TABLE 15.11A

INCIDENCE OF GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN BY PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO PREFERRED TERM	PLACEBO (N=243)	PRIOR TREATMENT SB 207499 (N=480)	Total (N=723)
TOTAL	41 (16.9%)	53 (11.0%)	94 (13.0%)
ABDOMINAL PAIN	22 (9.1%)	22 (4.6%)	44 (6.1%)
DIARRHEA	17 (7.0%)	14 (2.9%)	31 (4.3%)
NAUSEA	8 (3.3%)	6 (1.3%)	14 (1.9%)
VOMITING	9 (3.7%)	5 (1.0%)	14 (1.9%)
DYSPEPSIA	7 (2.9%)	3 (0.6%)	10 (1.4%)
GASTRITIS	3 (1.2%)	2 (0.4%)	5 (0.7%)
MELENA	3 (1.2%)	2 (0.4%)	5 (0.7%)
CONSTIPATION	0 .	3 (0.6%)	3 (0.4%)
GI HEMORRHAGE	2 (0.8%)	1 (0.2%)	3 (0.4%)
GASTROENTERITIS	0 .	2 (0.4%)	2 (0.3%)
HEMORRHOIDS	0 .	2 (0.4%)	2 (0.3%)
INTESTINAL OBSTRUCTION	1 (0.4%)	1 (0.2%)	2 (0.3%)
NEOPLASM NOS	0 .	2 (0.4%)	2 (0.3%)
ANOREXIA	1 (0.4%)	0 .	1 (0.1%)
DIARRHEA BLOODY	0 .	1 (0.2%)	1 (0.1%)
DUODENAL ULCER	0 .	1 (0.2%)	1 (0.1%)
GASTRIC ULCER	0 .	1 (0.2%)	1 (0.1%)
GASTROESOPHAGEAL REFLUX	1 (0.4%)	0 .	1 (0.1%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AN ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091
5. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO THE TOTAL GROUP

TABLE 15.11A

INCIDENCE OF GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN BY PREFERRED TERM, DESCENDING FREQUENCY OF OCCURRENCE AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO PREFERRED TERM	PLACEBO		PRIOR TREATMENT		Total	
	(N=243)		SB 207499 (N=480)		(N=723)	
GASTROINTESTINAL DISORDER NOS	0	.	1	(0.2%)	1	(0.1%)
INFECTION BACTERIAL	0	.	1	(0.2%)	1	(0.1%)
INJURY	0	.	1	(0.2%)	1	(0.1%)
PERITONITIS	0	.	1	(0.2%)	1	(0.1%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AN ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091
5. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO THE TOTAL GROUP

TABLE 15.11B

INCIDENCE OF GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN LEADING TO PATIENT WITHDRAWAL BY PREFERRED TERM,
DESCENDING FREQUENCY OF OCCURRENCE AND PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

WHO PREFERRED TERM	PLACEBO (N=243)		PRIOR TREATMENT SB 207499 (N=480)		Total (N=723)	
TOTAL	18	(7.4%)	13	(2.7%)	31	(4.3%)
ABDOMINAL PAIN	12	(4.9%)	8	(1.7%)	20	(2.8%)
DIARRHEA	6	(2.5%)	3	(0.6%)	9	(1.2%)
VOMITING	6	(2.5%)	1	(0.2%)	7	(1.0%)
NAUSEA	4	(1.6%)	1	(0.2%)	5	(0.7%)
DYSPEPSIA	2	(0.8%)	0	.	2	(0.3%)
GASTRITIS	0	.	2	(0.4%)	2	(0.3%)
GI HEMORRHAGE	1	(0.4%)	1	(0.2%)	2	(0.3%)
ANOREXIA	1	(0.4%)	0	.	1	(0.1%)
GASTROINTESTINAL DISORDER NOS	0	.	1	(0.2%)	1	(0.1%)
PERITONITIS	0	.	1	(0.2%)	1	(0.1%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER PREFERRED TERM
2. TOTAL ROW REPRESENTS TOTAL NUMBER OF PATIENTS WITH AN ADVERSE EXPERIENCE
3. PERCENTAGES ARE BASED ON NUMBER OF PATIENTS ENROLLED IN EACH TREATMENT GROUP
4. TREATMENT COLUMNS REPRESENT PRIOR TREATMENT DURING 24 WEEK DOUBLE-BLIND PHASE OF STUDIES 042 OR 091
5. ADVERSE EXPERIENCES ARE PRESENTED BY DESCENDING FREQUENCY OF OCCURRENCE WITH RESPECT TO THE TOTAL GROUP

TABLE 15.12A

NUMBER AND PERCENT OF PATIENTS WITH GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN AND ON-THERAPY POSITIVE
FECAL OCCULT BLOOD BY PRIOR TREATMENT IN STUDIES 042/091 AND BASELINE RESULT
PROTOCOL 040

		-----ON-THERAPY-----				
PRIOR TREATMENT	BASELINE	NEGATIVE		POSITIVE		TOTAL

PLACEBO	NEGATIVE	24	(96.0%)	1	(4.0%)	25
	POSITIVE	0		0		0
	TOTAL	24	(96.0%)	1	(4.0%)	25
SB 207499	NEGATIVE	40	(95.2%)	2	(4.8%)	42
	POSITIVE	0		0		0
	TOTAL	40	(95.2%)	2	(4.8%)	42
TOTAL	NEGATIVE	64	(95.5%)	3	(4.5%)	67
	POSITIVE	0		0		0
	TOTAL	64	(95.5%)	3	(4.5%)	67

1. ONLY PATIENTS WITH GASTROINTESTINAL ADVERSE EXPERIENCES OF CONCERN ARE INCLUDED IN THE SUMMARY

TABLE 15.12B

NUMBER AND PERCENT OF PATIENTS WITH ON-THERAPY POSITIVE FECAL OCCULT BLOOD BY PRIOR TREATMENT
IN STUDIES 042/091 AND BASELINE RESULT
PROTOCOL 040

PRIOR TREATMENT BASELINE		-----ON-THERAPY-----				TOTAL
		NEGATIVE		POSITIVE		
PLACEBO	NEGATIVE	190	(96.9%)	6	(3.1%)	196
	POSITIVE	1	(100.0%)	0		1
	MISSING	1	(100.0%)	0		1
	TOTAL	192	(97.0%)	6	(3.0%)	198
SB 207499	NEGATIVE	396	(95.0%)	21	(5.0%)	417
	POSITIVE	0		0		0
	MISSING	2	(100.0%)	0		2
	TOTAL	398	(95.0%)	21	(5.0%)	419
TOTAL	NEGATIVE	586	(95.6%)	27	(4.4%)	613
	POSITIVE	1	(100.0%)	0		1
	MISSING	3	(100.0%)	0		3
	TOTAL	590	(95.6%)	27	(4.4%)	617

TABLE 15.13A

TRANSITIONS FROM BASELINE IN ORTHOSTATIC VITAL SIGNS FOR PATIENTS WITH GASTROINTESTINAL ADVERSE EXPERIENCES
OF CONCERN BY PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	PARAMETER: SYSTOLIC BP TIME POINT: TOTAL ON-THERAPY			
			-----ON-THERAPY-----			
			NORMAL	HIGH	CONCERN	
PLACEBO	NORMAL (DECREASE<10 MM HG)	33	23 (69.7%)	8 (24.2%)	2 (6.1%)	
	HIGH (DECREASE 10-19 MM HG)	1	0	0	1 (100.0%)	
	CONCERN (DECREASE>=20 MM HG)	0	0	0	0	
	TOTAL	34	23 (67.6%)	8 (23.5%)	3 (8.8%)	
SB 207499	NORMAL (DECREASE<10 MM HG)	41	26 (63.4%)	13 (31.7%)	2 (4.9%)	
	HIGH (DECREASE 10-19 MM HG)	7	4 (57.1%)	3 (42.9%)	0	
	CONCERN (DECREASE>=20 MM HG)	0	0	0	0	
	TOTAL	48	30 (62.5%)	16 (33.3%)	2 (4.2%)	
TOTAL	NORMAL (DECREASE<10 MM HG)	74	49 (66.2%)	21 (28.4%)	4 (5.4%)	
	HIGH (DECREASE 10-19 MM HG)	8	4 (50.0%)	3 (37.5%)	1 (12.5%)	
	CONCERN (DECREASE>=20 MM HG)	0	0	0	0	
	TOTAL	82	53 (64.6%)	24 (29.3%)	5 (6.1%)	

1. PATIENTS ARE ASSIGNED TO A CATEGORY BASED ON THEIR HIGHEST ON-THERAPY VALUE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ORTHOSTATIC VITAL SIGNS ASSESSMENT COLLECTED DURING EXTENSION PERIOD

TABLE 15.13A

TRANSITIONS FROM BASELINE IN ORTHOSTATIC VITAL SIGNS FOR PATIENTS WITH GASTROINTESTINAL ADVERSE EXPERIENCES
OF CONCERN BY PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PARAMETER: SYSTOLIC BP TIME POINT: ENDPOINT

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL (DECREASE<10 MM HG)	33	25	(75.8%)	7	(21.2%)	1	(3.0%)
	HIGH (DECREASE 10-19 MM HG)	1	1	(100.0%)	0		0	
	CONCERN (DECREASE>=20 MM HG)	0	0		0		0	
	TOTAL	34	26	(76.5%)	7	(20.6%)	1	(2.9%)
SB 207499	NORMAL (DECREASE<10 MM HG)	41	34	(82.9%)	6	(14.6%)	1	(2.4%)
	HIGH (DECREASE 10-19 MM HG)	7	5	(71.4%)	2	(28.6%)	0	
	CONCERN (DECREASE>=20 MM HG)	0	0		0		0	
	TOTAL	48	39	(81.3%)	8	(16.7%)	1	(2.1%)
TOTAL	NORMAL (DECREASE<10 MM HG)	74	59	(79.7%)	13	(17.6%)	2	(2.7%)
	HIGH (DECREASE 10-19 MM HG)	8	6	(75.0%)	2	(25.0%)	0	
	CONCERN (DECREASE>=20 MM HG)	0	0		0		0	
	TOTAL	82	65	(79.3%)	15	(18.3%)	2	(2.4%)

1. PATIENTS ARE ASSIGNED TO A CATEGORY BASED ON THEIR HIGHEST ON-THERAPY VALUE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ORTHOSTATIC VITAL SIGNS ASSESSMENT COLLECTED DURING EXTENSION PERIOD

TABLE 15.13A

TRANSITIONS FROM BASELINE IN ORTHOSTATIC VITAL SIGNS FOR PATIENTS WITH GASTROINTESTINAL ADVERSE EXPERIENCES
OF CONCERN BY PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PARAMETER: DIASTOLIC BP TIME POINT: TOTAL ON-THERAPY

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (DECREASE<10 MM HG)	33	28	(84.8%)	5	(15.2%)
	CONCERN (DECREASE>=10 MM HG)	1	0		1	(100.0%)
	TOTAL	34	28	(82.4%)	6	(17.6%)
SB 207499	NORMAL (DECREASE<10 MM HG)	46	37	(80.4%)	9	(19.6%)
	CONCERN (DECREASE>=10 MM HG)	2	2	(100.0%)	0	
	TOTAL	48	39	(81.3%)	9	(18.8%)
TOTAL	NORMAL (DECREASE<10 MM HG)	79	65	(82.3%)	14	(17.7%)
	CONCERN (DECREASE>=10 MM HG)	3	2	(66.7%)	1	(33.3%)
	TOTAL	82	67	(81.7%)	15	(18.3%)

1. PATIENTS ARE ASSIGNED TO A CATEGORY BASED ON THEIR HIGHEST ON-THERAPY VALUE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ORTHOSTATIC VITAL SIGNS ASSESSMENT COLLECTED DURING EXTENSION PERIOD

TABLE 15.13A

TRANSITIONS FROM BASELINE IN ORTHOSTATIC VITAL SIGNS FOR PATIENTS WITH GASTROINTESTINAL ADVERSE EXPERIENCES
OF CONCERN BY PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PARAMETER: DIASTOLIC BP TIME POINT: ENDPOINT

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (DECREASE<10 MM HG)	33	30	(90.9%)	3	(9.1%)
	CONCERN (DECREASE>=10 MM HG)	1	0		1	(100.0%)
	TOTAL	34	30	(88.2%)	4	(11.8%)
SB 207499	NORMAL (DECREASE<10 MM HG)	46	45	(97.8%)	1	(2.2%)
	CONCERN (DECREASE>=10 MM HG)	2	2	(100.0%)	0	
	TOTAL	48	47	(97.9%)	1	(2.1%)
TOTAL	NORMAL (DECREASE<10 MM HG)	79	75	(94.9%)	4	(5.1%)
	CONCERN (DECREASE>=10 MM HG)	3	2	(66.7%)	1	(33.3%)
	TOTAL	82	77	(93.9%)	5	(6.1%)

1. PATIENTS ARE ASSIGNED TO A CATEGORY BASED ON THEIR HIGHEST ON-THERAPY VALUE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ORTHOSTATIC VITAL SIGNS ASSESSMENT COLLECTED DURING EXTENSION PERIOD

TABLE 15.13A

TRANSITIONS FROM BASELINE IN ORTHOSTATIC VITAL SIGNS FOR PATIENTS WITH GASTROINTESTINAL ADVERSE EXPERIENCES
OF CONCERN BY PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PARAMETER: HEART RATE TIME POINT: TOTAL ON-THERAPY

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (INCREASE<10 BPM)	33	32	(97.0%)	1	(3.0%)
	CONCERN (INCREASE>=10 BPM)	1	1	(100.0%)	0	
	TOTAL	34	33	(97.1%)	1	(2.9%)
SB 207499	NORMAL (INCREASE<10 BPM)	45	38	(84.4%)	7	(15.6%)
	CONCERN (INCREASE>=10 BPM)	3	1	(33.3%)	2	(66.7%)
	TOTAL	48	39	(81.3%)	9	(18.8%)
TOTAL	NORMAL (INCREASE<10 BPM)	78	70	(89.7%)	8	(10.3%)
	CONCERN (INCREASE>=10 BPM)	4	2	(50.0%)	2	(50.0%)
	TOTAL	82	72	(87.8%)	10	(12.2%)

1. PATIENTS ARE ASSIGNED TO A CATEGORY BASED ON THEIR HIGHEST ON-THERAPY VALUE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ORTHOSTATIC VITAL SIGNS ASSESSMENT COLLECTED DURING EXTENSION PERIOD

TABLE 15.13A

TRANSITIONS FROM BASELINE IN ORTHOSTATIC VITAL SIGNS FOR PATIENTS WITH GASTROINTESTINAL ADVERSE EXPERIENCES
OF CONCERN BY PRIOR TREATMENT IN STUDIES 042/091
PROTOCOL 040

PARAMETER: HEART RATE TIME POINT: ENDPOINT

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (INCREASE<10 BPM)	33	33	(100.0%)	0	
	CONCERN (INCREASE>=10 BPM)	1	1	(100.0%)	0	
	TOTAL	34	34	(100.0%)	0	
SB 207499	NORMAL (INCREASE<10 BPM)	45	42	(93.3%)	3	(6.7%)
	CONCERN (INCREASE>=10 BPM)	3	2	(66.7%)	1	(33.3%)
	TOTAL	48	44	(91.7%)	4	(8.3%)
TOTAL	NORMAL (INCREASE<10 BPM)	78	75	(96.2%)	3	(3.8%)
	CONCERN (INCREASE>=10 BPM)	4	3	(75.0%)	1	(25.0%)
	TOTAL	82	78	(95.1%)	4	(4.9%)

1. PATIENTS ARE ASSIGNED TO A CATEGORY BASED ON THEIR HIGHEST ON-THERAPY VALUE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ORTHOSTATIC VITAL SIGNS ASSESSMENT COLLECTED DURING EXTENSION PERIOD

TABLE 15.13B

TRANSITIONS FROM BASELINE IN ORTHOSTATIC VITAL SIGNS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PRIOR TREATMENT	BASELINE	PARAMETER: SYSTOLIC BP	TIME POINT: TOTAL ON-THERAPY	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
					NORMAL	HIGH	CONCERN	
PLACEBO	NORMAL (DECREASE<10 MM HG)			197	154 (78.2%)	35 (17.8%)	8 (4.1%)	
	HIGH (DECREASE 10-19 MM HG)			23	12 (52.2%)	8 (34.8%)	3 (13.0%)	
	CONCERN (DECREASE>=20 MM HG)			0	0	0	0	
	TOTAL			220	166 (75.5%)	43 (19.5%)	11 (5.0%)	
SB 207499	NORMAL (DECREASE<10 MM HG)			410	299 (72.9%)	94 (22.9%)	17 (4.1%)	
	HIGH (DECREASE 10-19 MM HG)			41	27 (65.9%)	11 (26.8%)	3 (7.3%)	
	CONCERN (DECREASE>=20 MM HG)			0	0	0	0	
	TOTAL			451	326 (72.3%)	105 (23.3%)	20 (4.4%)	
TOTAL	NORMAL (DECREASE<10 MM HG)			607	453 (74.6%)	129 (21.3%)	25 (4.1%)	
	HIGH (DECREASE 10-19 MM HG)			64	39 (60.9%)	19 (29.7%)	6 (9.4%)	
	CONCERN (DECREASE>=20 MM HG)			0	0	0	0	
	TOTAL			671	492 (73.3%)	148 (22.1%)	31 (4.6%)	

1. PATIENTS ARE ASSIGNED TO A CATEGORY BASED ON THEIR HIGHEST ON-THERAPY VALUE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ORTHOSTATIC VITAL SIGNS ASSESSMENT COLLECTED DURING EXTENSION PERIOD

TABLE 15.13B

TRANSITIONS FROM BASELINE IN ORTHOSTATIC VITAL SIGNS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: SYSTOLIC BP TIME POINT: ENDPOINT

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL (DECREASE<10 MM HG)	197	179	(90.9%)	16	(8.1%)	2	(1.0%)
	HIGH (DECREASE 10-19 MM HG)	23	22	(95.7%)	0		1	(4.3%)
	CONCERN (DECREASE>=20 MM HG)	0	0		0		0	
	TOTAL	220	201	(91.4%)	16	(7.3%)	3	(1.4%)
SB 207499	NORMAL (DECREASE<10 MM HG)	410	362	(88.3%)	40	(9.8%)	8	(2.0%)
	HIGH (DECREASE 10-19 MM HG)	41	34	(82.9%)	6	(14.6%)	1	(2.4%)
	CONCERN (DECREASE>=20 MM HG)	0	0		0		0	
	TOTAL	451	396	(87.8%)	46	(10.2%)	9	(2.0%)
TOTAL	NORMAL (DECREASE<10 MM HG)	607	541	(89.1%)	56	(9.2%)	10	(1.6%)
	HIGH (DECREASE 10-19 MM HG)	64	56	(87.5%)	6	(9.4%)	2	(3.1%)
	CONCERN (DECREASE>=20 MM HG)	0	0		0		0	
	TOTAL	671	597	(89.0%)	62	(9.2%)	12	(1.8%)

1. PATIENTS ARE ASSIGNED TO A CATEGORY BASED ON THEIR HIGHEST ON-THERAPY VALUE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ORTHOSTATIC VITAL SIGNS ASSESSMENT COLLECTED DURING EXTENSION PERIOD

TABLE 15.13B

TRANSITIONS FROM BASELINE IN ORTHOSTATIC VITAL SIGNS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: DIASTOLIC BP TIME POINT: TOTAL ON-THERAPY

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	
PLACEBO	NORMAL (DECREASE<10 MM HG)	218	196	(89.9%)	22	(10.1%)
	CONCERN (DECREASE>=10 MM HG)	2	1	(50.0%)	1	(50.0%)
	TOTAL	220	197	(89.5%)	23	(10.5%)
SB 207499	NORMAL (DECREASE<10 MM HG)	445	389	(87.4%)	56	(12.6%)
	CONCERN (DECREASE>=10 MM HG)	6	5	(83.3%)	1	(16.7%)
	TOTAL	451	394	(87.4%)	57	(12.6%)
TOTAL	NORMAL (DECREASE<10 MM HG)	663	585	(88.2%)	78	(11.8%)
	CONCERN (DECREASE>=10 MM HG)	8	6	(75.0%)	2	(25.0%)
	TOTAL	671	591	(88.1%)	80	(11.9%)

1. PATIENTS ARE ASSIGNED TO A CATEGORY BASED ON THEIR HIGHEST ON-THERAPY VALUE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ORTHOSTATIC VITAL SIGNS ASSESSMENT COLLECTED DURING EXTENSION PERIOD

TABLE 15.13B

TRANSITIONS FROM BASELINE IN ORTHOSTATIC VITAL SIGNS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: DIASTOLIC BP TIME POINT: ENDPOINT

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (DECREASE<10 MM HG)	218	213	(97.7%)	5	(2.3%)
	CONCERN (DECREASE>=10 MM HG)	2	1	(50.0%)	1	(50.0%)
	TOTAL	220	214	(97.3%)	6	(2.7%)
SB 207499	NORMAL (DECREASE<10 MM HG)	445	424	(95.3%)	21	(4.7%)
	CONCERN (DECREASE>=10 MM HG)	6	5	(83.3%)	1	(16.7%)
	TOTAL	451	429	(95.1%)	22	(4.9%)
TOTAL	NORMAL (DECREASE<10 MM HG)	663	637	(96.1%)	26	(3.9%)
	CONCERN (DECREASE>=10 MM HG)	8	6	(75.0%)	2	(25.0%)
	TOTAL	671	643	(95.8%)	28	(4.2%)

1. PATIENTS ARE ASSIGNED TO A CATEGORY BASED ON THEIR HIGHEST ON-THERAPY VALUE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ORTHOSTATIC VITAL SIGNS ASSESSMENT COLLECTED DURING EXTENSION PERIOD

TABLE 15.13B

TRANSITIONS FROM BASELINE IN ORTHOSTATIC VITAL SIGNS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: HEART RATE TIME POINT: TOTAL ON-THERAPY

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (INCREASE<10 BPM)	215	195	(90.7%)	20	(9.3%)
	CONCERN (INCREASE>=10 BPM)	5	4	(80.0%)	1	(20.0%)
	MISSING	0	0		0	
	TOTAL	220	199	(90.5%)	21	(9.5%)
SB 207499	NORMAL (INCREASE<10 BPM)	444	388	(87.4%)	56	(12.6%)
	CONCERN (INCREASE>=10 BPM)	6	4	(66.7%)	2	(33.3%)
	MISSING	1	1	(100.0%)	0	
	TOTAL	451	393	(87.1%)	58	(12.9%)
TOTAL	NORMAL (INCREASE<10 BPM)	659	583	(88.5%)	76	(11.5%)
	CONCERN (INCREASE>=10 BPM)	11	8	(72.7%)	3	(27.3%)
	MISSING	1	1	(100.0%)	0	
	TOTAL	671	592	(88.2%)	79	(11.8%)

1. PATIENTS ARE ASSIGNED TO A CATEGORY BASED ON THEIR HIGHEST ON-THERAPY VALUE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ORTHOSTATIC VITAL SIGNS ASSESSMENT COLLECTED DURING EXTENSION PERIOD

TABLE 15.13B

TRANSITIONS FROM BASELINE IN ORTHOSTATIC VITAL SIGNS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: HEART RATE TIME POINT: ENDPOINT

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	
PLACEBO	NORMAL (INCREASE<10 BPM)	215	209	(97.2%)	6	(2.8%)
	CONCERN (INCREASE>=10 BPM)	5	4	(80.0%)	1	(20.0%)
	MISSING	0	0		0	
	TOTAL	220	213	(96.8%)	7	(3.2%)
SB 207499	NORMAL (INCREASE<10 BPM)	444	423	(95.3%)	21	(4.7%)
	CONCERN (INCREASE>=10 BPM)	6	5	(83.3%)	1	(16.7%)
	MISSING	1	1	(100.0%)	0	
	TOTAL	451	429	(95.1%)	22	(4.9%)
TOTAL	NORMAL (INCREASE<10 BPM)	659	632	(95.9%)	27	(4.1%)
	CONCERN (INCREASE>=10 BPM)	11	9	(81.8%)	2	(18.2%)
	MISSING	1	1	(100.0%)	0	
	TOTAL	671	642	(95.7%)	29	(4.3%)

1. PATIENTS ARE ASSIGNED TO A CATEGORY BASED ON THEIR HIGHEST ON-THERAPY VALUE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ORTHOSTATIC VITAL SIGNS ASSESSMENT COLLECTED DURING EXTENSION PERIOD

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Hemoglobin (G/L)	BASELINE	PLACEBO	243	148.76	13.82	108.0	237.7	0	.	.	.	.
		SB 207499	478	149.84	12.96	108.0	189.3	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	236	148.88	12.29	108.8	185.3	236	0.23	10.39	-96.7	35.4
		SB 207499	468	149.03	12.73	115.2	194.2	466	-0.84	7.42	-33.0	20.9
	VISIT 2/WEEK 1	PLACEBO	234	148.74	12.57	106.3	186.1	234	-0.05	10.02	-89.4	37.1
		SB 207499	450	148.26	12.72	113.6	195.8	448	-1.53	7.68	-31.4	18.5
	VISIT 3/WEEK 2	PLACEBO	219	149.13	13.11	110.4	187.7	219	0.06	10.34	-93.5	40.3
		SB 207499	452	148.68	12.62	108.8	186.1	451	-1.21	7.84	-29.0	37.9
	VISIT 4/WEEK 4	PLACEBO	213	149.38	12.46	115.2	181.3	213	0.33	10.47	-88.6	48.3
		SB 207499	445	148.76	12.48	110.4	190.1	444	-1.26	8.20	-33.0	26.6
	VISIT 5/WEEK 8	PLACEBO	205	148.85	12.84	113.6	182.1	205	-0.54	9.83	-84.6	20.1
		SB 207499	437	149.31	12.95	111.2	187.7	436	-0.56	8.02	-35.4	28.2
	VISIT 6/WEEK 12	PLACEBO	203	149.43	12.69	113.6	178.9	203	0.38	10.43	-85.4	51.6
		SB 207499	428	149.49	13.00	111.2	195.0	427	-0.58	8.10	-30.6	27.4
	VISIT 7/WEEK 16	PLACEBO	195	149.19	12.26	103.9	181.3	195	0.12	10.29	-83.8	47.5
		SB 207499	421	149.40	12.48	106.3	195.0	420	-0.57	8.27	-35.4	25.0
	VISIT 8/WEEK 20	PLACEBO	194	149.24	13.09	110.4	186.1	194	0.18	10.59	-83.8	47.5
		SB 207499	423	149.21	12.87	104.7	195.0	422	-1.05	7.94	-37.1	33.0
	VISIT 9/WEEK 24	PLACEBO	187	149.22	12.57	112.8	186.9	187	0.36	10.77	-87.0	50.0
		SB 207499	422	149.70	13.24	103.9	190.1	421	-0.51	7.83	-33.0	29.0
	VISIT 10/WEEK 28	PLACEBO	185	149.33	13.63	95.9	193.4	185	0.32	12.00	-93.5	50.0
		SB 207499	413	149.73	13.05	103.1	190.1	412	-0.47	8.64	-43.5	46.7
	VISIT 11/WEEK 32	PLACEBO	185	148.59	12.82	103.9	190.9	185	-0.05	10.93	-88.6	40.3
		SB 207499	410	149.46	13.19	103.1	195.0	409	-0.71	8.45	-45.1	30.6
	VISIT 12/WEEK 36	PLACEBO	181	148.13	13.20	108.0	189.3	181	-0.39	11.43	-87.8	41.9
		SB 207499	408	149.29	13.11	103.1	198.2	407	-0.87	8.58	-45.1	23.4
	VISIT 13/WEEK 40	PLACEBO	179	147.73	12.78	113.6	178.9	179	-0.61	11.14	-83.8	35.4
		SB 207499	398	149.17	13.84	91.0	195.8	397	-1.05	9.09	-55.6	34.6
	VISIT 14/WEEK 44	PLACEBO	182	147.98	12.98	102.3	182.9	182	-0.85	10.87	-80.6	35.4
		SB 207499	399	149.14	13.41	103.1	195.8	398	-1.09	8.64	-45.9	29.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Hemoglobin (G/L)	VISIT 15/WEEK 48	PLACEBO	181	148.61	12.72	110.4	187.7	181	-0.07	11.70	-87.8	37.9
		SB 207499	397	149.15	13.34	104.7	195.0	396	-0.85	9.19	-51.6	27.4
	VISIT 16/WEEK 52	PLACEBO	176	148.57	13.21	103.1	194.2	176	-0.25	12.45	-91.0	37.1
		SB 207499	376	149.45	12.54	103.9	186.9	375	-0.60	9.31	-52.4	32.2
	VISIT 17/WEEK 56	PLACEBO	166	148.02	13.04	103.9	182.9	166	-0.27	9.31	-37.1	37.9
		SB 207499	356	149.53	13.00	100.7	197.4	356	-0.44	8.56	-35.4	33.8
	VISIT 18/WEEK 60	PLACEBO	169	148.05	12.53	115.2	183.7	169	-0.24	9.10	-25.0	41.9
		SB 207499	366	149.92	13.13	102.3	186.9	366	-0.17	9.31	-38.7	30.6
	VISIT 19/WEEK 64	PLACEBO	138	147.71	13.42	95.1	185.3	138	-0.28	10.22	-50.0	32.2
		SB 207499	296	149.35	13.36	100.7	195.8	296	-0.25	9.17	-37.1	27.4
	VISIT 20/WEEK 68	PLACEBO	138	147.72	13.36	99.9	182.9	138	-0.16	9.58	-45.1	36.3
		SB 207499	294	149.05	13.28	99.9	187.7	294	-0.58	8.66	-37.9	31.4
	VISIT 21/WEEK 72	PLACEBO	169	148.01	13.20	112.8	183.7	169	-0.21	9.39	-32.2	34.6
		SB 207499	351	149.54	13.16	96.7	187.7	350	-0.70	9.01	-41.1	30.6
	VISIT 22/WEEK 76	PLACEBO	98	147.82	12.75	116.8	185.3	98	0.61	8.09	-21.8	30.6
		SB 207499	195	148.22	15.05	96.7	195.0	195	-0.76	9.32	-41.1	38.7
	VISIT 23/WEEK 80	PLACEBO	99	147.08	13.14	108.8	183.7	99	0.21	9.20	-25.0	31.4
		SB 207499	188	147.65	15.08	91.8	199.0	188	-1.32	9.79	-45.9	42.7
	VISIT 24/WEEK 84	PLACEBO	161	147.10	14.21	83.8	181.3	161	-1.11	10.65	-70.1	30.6
		SB 207499	332	148.41	13.74	87.8	197.4	331	-1.32	9.18	-50.0	41.1
	VISIT 25/WEEK 88	PLACEBO	51	145.82	15.75	110.4	178.9	51	-1.42	10.79	-47.5	17.7
		SB 207499	95	147.13	16.26	94.3	189.3	95	-2.31	11.36	-43.5	31.4
	VISIT 26/WEEK 92	PLACEBO	52	144.12	16.15	108.8	175.6	52	-2.43	10.21	-49.1	20.1
		SB 207499	95	146.85	16.61	90.2	195.8	95	-2.46	11.30	-47.5	39.5
	VISIT 27/WEEK 96	PLACEBO	155	146.44	13.06	108.0	181.3	155	-1.59	9.55	-37.1	23.4
		SB 207499	326	146.90	13.74	88.6	197.4	326	-2.82	9.54	-49.1	41.1
	VISIT 28/WEEK 10	PLACEBO	20	142.52	15.31	120.0	178.9	20	-0.52	10.73	-36.3	14.5
		SB 207499	48	145.25	14.40	86.2	173.2	48	-3.42	10.63	-51.6	11.3
	VISIT 29/WEEK 10	PLACEBO	18	145.24	12.94	125.7	174.8	18	-0.94	9.90	-32.2	13.7
		SB 207499	39	147.54	11.83	120.8	173.2	39	-2.46	8.82	-24.2	12.1

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Hemoglobin (G/L)	VISIT 30/WEEK 10	PLACEBO	128	147.01	13.05	107.2	177.2	128	-0.92	9.19	-30.6	26.6
		SB 207499	268	147.55	12.29	102.3	193.4	268	-1.83	9.81	-36.3	32.2
	VISIT 31/WEEK 11	PLACEBO	8	151.56	13.39	125.7	171.6	8	3.02	3.85	-3.2	8.1
		SB 207499	17	146.63	15.34	116.8	171.6	17	-4.03	13.77	-41.1	19.3
	VISIT 32/WEEK 11	PLACEBO	9	148.15	14.96	125.7	170.8	9	-1.43	11.15	-29.8	6.4
		SB 207499	16	148.99	14.61	125.7	177.2	16	-2.77	11.02	-25.0	13.7
	VISIT 33/WEEK 12	PLACEBO	89	144.56	14.14	99.9	189.3	89	-3.41	10.54	-33.0	46.7
		SB 207499	184	146.91	12.58	95.1	182.1	184	-1.64	9.59	-33.0	25.0
	VISIT 34/WEEK 12	PLACEBO	3	152.54	3.63	149.0	156.3	3	3.49	4.86	-1.6	8.1
		SB 207499	3	157.10	12.17	144.2	168.4	3	2.95	8.87	-7.3	8.9
	VISIT 35/WEEK 12	PLACEBO	3	147.17	1.68	145.8	149.0	3	-1.88	8.98	-12.1	4.8
		SB 207499	3	153.34	14.19	141.8	169.2	3	-0.81	5.64	-6.4	4.8
	VISIT 36/WEEK 13	PLACEBO	33	145.29	13.61	90.2	166.0	33	-2.56	9.65	-27.4	11.3
		SB 207499	58	145.36	15.86	104.7	182.1	58	-3.88	10.37	-32.2	22.6
	VISIT 37/WEEK 13	PLACEBO	1	146.63	.	146.6	146.6	1	2.42	.	2.4	2.4
		SB 207499	2	159.12	21.08	144.2	174.0	2	15.71	11.96	7.3	24.2
	ENDPOINT	PLACEBO	239	147.14	14.91	83.8	189.3	239	-1.68	12.22	-91.0	46.7
		SB 207499	472	147.29	13.97	86.2	197.4	470	-2.56	10.04	-51.6	41.1

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Hematocrit (%)	BASELINE	PLACEBO	243	44.41	4.23	32.0	73.1	0	.	.	.	.
		SB 207499	478	44.65	3.79	32.4	57.8	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	236	44.66	3.79	33.1	57.4	236	0.29	3.23	-30.4	10.5
		SB 207499	468	44.76	3.94	34.4	62.1	466	0.11	2.58	-8.4	7.5
	VISIT 2/WEEK 1	PLACEBO	234	44.63	3.93	31.9	57.2	234	0.22	3.28	-29.4	11.9
		SB 207499	450	44.50	3.90	33.9	64.7	448	-0.13	2.52	-7.6	9.2
	VISIT 3/WEEK 2	PLACEBO	219	44.81	4.03	33.2	57.7	219	0.28	3.33	-29.4	11.7
		SB 207499	452	44.72	3.90	32.3	61.1	451	0.06	2.58	-9.9	11.6
	VISIT 4/WEEK 4	PLACEBO	213	44.94	4.02	34.6	56.0	213	0.39	3.42	-28.6	14.8
		SB 207499	445	44.80	3.89	34.0	59.7	444	0.11	2.60	-9.3	9.3
	VISIT 5/WEEK 8	PLACEBO	205	44.86	4.11	34.0	55.9	205	0.23	3.15	-26.5	6.9
		SB 207499	437	44.87	3.94	33.3	56.5	436	0.21	2.52	-7.8	8.7
	VISIT 6/WEEK 12	PLACEBO	204	44.91	4.03	34.0	55.0	204	0.37	3.31	-26.8	14.2
		SB 207499	429	44.94	3.96	33.4	59.7	428	0.24	2.63	-7.4	10.0
	VISIT 7/WEEK 16	PLACEBO	195	44.98	3.81	31.1	56.1	195	0.40	3.21	-26.4	14.1
		SB 207499	421	44.97	3.84	33.0	59.4	420	0.30	2.61	-8.9	8.6
	VISIT 8/WEEK 20	PLACEBO	194	44.98	4.13	32.8	57.6	194	0.40	3.40	-28.6	12.2
		SB 207499	423	45.06	3.95	32.9	59.6	422	0.29	2.56	-8.5	12.7
	VISIT 9/WEEK 24	PLACEBO	187	45.08	3.91	34.2	57.2	187	0.56	3.40	-28.3	13.3
		SB 207499	422	45.28	3.98	31.6	58.8	421	0.53	2.57	-8.8	8.6
	VISIT 10/WEEK 28	PLACEBO	185	45.04	4.17	30.0	59.1	185	0.46	3.70	-28.7	13.2
		SB 207499	413	45.20	3.96	30.7	58.7	412	0.44	2.81	-14.6	15.3
	VISIT 11/WEEK 32	PLACEBO	185	44.91	3.92	32.7	59.1	185	0.47	3.53	-29.0	10.4
		SB 207499	410	45.23	3.93	32.6	58.7	409	0.46	2.70	-11.9	9.9
	VISIT 12/WEEK 36	PLACEBO	181	44.70	3.99	32.8	57.9	181	0.29	3.54	-28.1	11.6
		SB 207499	408	45.18	4.01	30.6	59.9	407	0.42	2.74	-12.3	7.9
	VISIT 13/WEEK 40	PLACEBO	179	44.48	3.83	34.3	54.8	179	0.13	3.55	-25.9	7.5
		SB 207499	398	44.97	4.19	27.8	59.9	397	0.19	2.93	-14.8	12.6
	VISIT 14/WEEK 44	PLACEBO	182	44.44	3.87	29.1	55.7	182	-0.05	3.49	-26.2	8.9
		SB 207499	399	44.85	4.05	32.0	61.1	398	0.08	2.82	-12.4	10.1

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Hematocrit (%)	VISIT 15/WEEK 48	PLACEBO	181	44.67	3.93	32.2	57.9	181	0.21	3.79	-27.4	9.2
		SB 207499	397	44.83	4.10	31.8	60.2	396	0.13	2.99	-13.5	8.2
	VISIT 16/WEEK 52	PLACEBO	176	44.70	3.94	29.5	61.1	176	0.19	3.96	-28.1	12.4
		SB 207499	376	45.00	3.86	33.5	58.1	375	0.29	2.96	-13.5	10.2
	VISIT 17/WEEK 56	PLACEBO	166	44.38	3.91	31.4	56.4	166	0.09	2.88	-11.0	7.7
		SB 207499	356	44.95	3.97	30.0	62.1	356	0.26	2.72	-8.6	13.5
	VISIT 18/WEEK 60	PLACEBO	169	44.44	3.87	33.6	58.0	169	0.11	2.89	-7.7	9.3
		SB 207499	366	45.00	4.06	30.6	60.0	366	0.25	2.96	-10.4	13.3
	VISIT 19/WEEK 64	PLACEBO	138	44.20	4.05	30.3	57.5	138	0.15	3.23	-14.6	8.8
		SB 207499	296	44.76	3.98	32.2	59.0	296	0.21	2.91	-9.0	9.0
	VISIT 20/WEEK 68	PLACEBO	138	44.35	3.81	34.4	56.1	138	0.34	2.77	-10.5	8.7
		SB 207499	294	44.64	4.02	28.8	61.7	294	0.06	2.75	-12.1	14.2
	VISIT 21/WEEK 72	PLACEBO	169	44.53	3.93	34.4	56.5	169	0.23	2.79	-8.6	10.0
		SB 207499	351	44.99	3.98	31.8	61.2	350	0.18	2.79	-9.4	13.7
	VISIT 22/WEEK 76	PLACEBO	98	44.35	3.89	34.6	57.4	98	0.54	2.48	-5.5	9.1
		SB 207499	195	44.47	4.47	31.5	65.0	195	0.11	3.06	-9.7	17.5
	VISIT 23/WEEK 80	PLACEBO	99	44.29	4.16	31.7	57.0	99	0.58	2.89	-7.1	8.3
		SB 207499	188	44.49	4.54	30.1	63.7	188	0.11	3.10	-11.1	16.2
	VISIT 24/WEEK 84	PLACEBO	161	44.42	4.45	25.3	57.1	161	0.08	3.37	-19.7	8.4
		SB 207499	332	44.97	4.20	29.4	64.2	331	0.28	2.93	-11.8	16.7
	VISIT 25/WEEK 88	PLACEBO	51	44.00	4.93	33.4	54.4	51	0.22	3.31	-14.1	5.5
		SB 207499	95	44.61	5.01	31.2	63.3	95	-0.03	3.62	-10.0	15.8
	VISIT 26/WEEK 92	PLACEBO	52	43.46	4.87	32.6	54.8	52	-0.10	3.16	-13.6	7.1
		SB 207499	95	44.44	4.95	30.5	63.8	95	-0.20	3.57	-10.7	16.3
	VISIT 27/WEEK 96	PLACEBO	155	44.40	4.07	32.0	57.5	155	0.14	3.08	-9.3	8.8
		SB 207499	326	44.62	4.10	30.2	65.2	326	-0.05	3.00	-11.0	17.7
	VISIT 28/WEEK 10	PLACEBO	20	43.77	4.81	36.5	55.9	20	1.24	3.25	-8.9	7.2
		SB 207499	48	44.55	4.40	29.4	56.3	48	0.32	3.30	-11.8	6.4
	VISIT 29/WEEK 10	PLACEBO	18	44.24	3.56	39.1	52.4	18	0.85	3.02	-7.0	5.3
		SB 207499	39	44.99	3.67	36.5	52.9	39	0.22	2.98	-7.0	4.7

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Hematocrit (%)	VISIT 30/WEEK 10	PLACEBO	128	44.55	4.04	31.9	55.6	128	0.36	2.84	-8.6	8.9
		SB 207499	268	44.78	3.72	33.2	56.7	268	0.25	3.12	-11.6	9.4
	VISIT 31/WEEK 11	PLACEBO	8	46.49	3.97	38.6	52.4	8	3.10	1.03	1.3	4.5
		SB 207499	17	44.69	4.50	36.3	53.2	17	-0.08	4.13	-10.6	6.2
	VISIT 32/WEEK 11	PLACEBO	9	45.20	4.40	37.6	51.1	9	1.32	3.75	-7.6	5.1
		SB 207499	16	45.48	4.75	38.1	54.0	16	0.23	3.88	-6.1	8.4
	VISIT 33/WEEK 12	PLACEBO	89	43.61	4.23	31.0	56.6	89	-0.30	3.23	-9.3	14.5
		SB 207499	184	44.21	3.91	30.4	55.8	184	0.07	2.96	-9.9	8.2
	VISIT 34/WEEK 12	PLACEBO	3	46.23	1.77	44.2	47.4	3	3.20	1.90	1.6	5.3
		SB 207499	3	47.93	3.61	44.0	51.1	3	2.00	3.51	-1.9	4.9
	VISIT 35/WEEK 12	PLACEBO	3	43.33	0.72	42.5	43.8	3	0.30	2.21	-2.2	2.0
		SB 207499	3	45.97	4.60	42.2	51.1	3	0.03	1.69	-1.9	1.2
	VISIT 36/WEEK 13	PLACEBO	33	43.81	4.03	26.9	49.4	33	0.24	3.25	-7.8	5.0
		SB 207499	58	43.83	4.46	31.4	54.7	58	-0.51	3.13	-8.9	6.7
	VISIT 37/WEEK 13	PLACEBO	1	42.30	.	42.3	42.3	1	0.50	.	0.5	0.5
		SB 207499	2	47.00	6.36	42.5	51.5	2	4.60	4.38	1.5	7.7
ENDPOINT		PLACEBO	239	44.35	4.47	25.3	56.6	239	-0.08	3.66	-28.1	14.5
		SB 207499	472	44.35	4.26	29.4	65.2	470	-0.30	3.18	-11.8	17.7

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Red Blood Cell Count ($10^{12}/L$)	BASELINE	PLACEBO	243	4.70	0.48	3.3	7.6	0	.	.	.	.
		SB 207499	478	4.76	0.46	3.1	6.3	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	236	4.68	0.46	3.3	6.5	236	-0.02	0.34	-3.2	1.0
		SB 207499	468	4.73	0.46	3.3	6.2	466	-0.03	0.26	-1.1	0.8
	VISIT 2/WEEK 1	PLACEBO	234	4.69	0.46	3.2	6.5	234	-0.02	0.33	-3.0	1.0
		SB 207499	450	4.72	0.46	3.3	6.3	448	-0.04	0.26	-1.1	0.8
	VISIT 3/WEEK 2	PLACEBO	219	4.70	0.49	3.3	6.7	219	-0.01	0.36	-3.1	1.7
		SB 207499	452	4.73	0.45	3.0	6.1	451	-0.03	0.26	-1.1	0.8
	VISIT 4/WEEK 4	PLACEBO	213	4.73	0.46	3.4	6.7	213	0.00	0.35	-3.0	0.8
		SB 207499	445	4.74	0.47	3.5	6.5	444	-0.03	0.28	-1.0	1.5
	VISIT 5/WEEK 8	PLACEBO	205	4.71	0.47	3.0	6.5	205	-0.02	0.35	-2.9	0.9
		SB 207499	437	4.75	0.45	3.1	6.1	436	-0.02	0.26	-0.9	0.7
	VISIT 6/WEEK 12	PLACEBO	204	4.72	0.46	3.1	6.6	204	-0.00	0.33	-2.8	0.7
		SB 207499	429	4.75	0.45	3.2	7.0	428	-0.02	0.27	-0.8	1.6
	VISIT 7/WEEK 16	PLACEBO	195	4.73	0.44	3.1	6.5	195	-0.00	0.33	-2.8	0.8
		SB 207499	421	4.76	0.46	3.2	6.2	420	-0.01	0.27	-0.9	1.0
	VISIT 8/WEEK 20	PLACEBO	194	4.73	0.45	3.0	6.1	194	0.01	0.34	-2.9	0.6
		SB 207499	423	4.76	0.46	3.1	6.2	422	-0.02	0.25	-1.0	0.9
	VISIT 9/WEEK 24	PLACEBO	187	4.74	0.45	3.0	6.6	187	0.02	0.34	-2.9	0.8
		SB 207499	422	4.78	0.46	2.9	6.2	421	0.01	0.24	-0.8	0.7
	VISIT 10/WEEK 28	PLACEBO	185	4.72	0.46	3.0	6.3	185	-0.00	0.36	-3.1	0.8
		SB 207499	413	4.77	0.46	2.8	6.0	412	-0.01	0.27	-1.4	1.1
	VISIT 11/WEEK 32	PLACEBO	185	4.71	0.44	3.0	6.5	185	-0.00	0.34	-3.1	0.9
		SB 207499	410	4.77	0.46	3.0	6.4	409	-0.01	0.27	-1.0	0.9
	VISIT 12/WEEK 36	PLACEBO	181	4.70	0.45	2.9	6.3	181	-0.02	0.35	-3.0	1.0
		SB 207499	408	4.77	0.45	2.7	6.2	407	-0.00	0.26	-1.0	0.8
	VISIT 13/WEEK 40	PLACEBO	179	4.69	0.44	3.4	6.3	179	-0.03	0.36	-2.8	0.7
		SB 207499	398	4.75	0.47	2.4	5.9	397	-0.02	0.28	-1.2	0.8
	VISIT 14/WEEK 44	PLACEBO	182	4.69	0.45	2.7	6.4	182	-0.04	0.34	-2.7	0.7
		SB 207499	399	4.75	0.46	2.9	5.9	398	-0.03	0.27	-0.9	0.8

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Red Blood Cell Count (10 ¹² /L)	VISIT 15/WEEK 48	PLACEBO	181	4.70	0.46	3.2	6.7	181	-0.02	0.37	-2.9	0.8
		SB 207499	397	4.75	0.48	2.9	5.9	396	-0.02	0.29	-1.2	0.9
	VISIT 16/WEEK 52	PLACEBO	176	4.71	0.44	3.5	6.4	176	-0.02	0.38	-2.9	1.1
		SB 207499	376	4.75	0.45	3.2	6.1	375	-0.01	0.29	-1.1	1.3
	VISIT 17/WEEK 56	PLACEBO	166	4.70	0.44	3.1	6.2	166	-0.01	0.28	-1.1	0.9
		SB 207499	356	4.77	0.46	2.8	6.6	356	0.01	0.27	-0.9	1.8
	VISIT 18/WEEK 60	PLACEBO	169	4.71	0.44	3.3	6.2	169	-0.01	0.30	-0.9	1.3
		SB 207499	366	4.79	0.47	2.8	6.6	366	0.02	0.30	-1.1	1.8
	VISIT 19/WEEK 64	PLACEBO	138	4.71	0.47	3.5	6.3	138	-0.01	0.30	-1.0	1.5
		SB 207499	296	4.77	0.47	2.9	5.9	296	0.02	0.28	-1.0	0.9
	VISIT 20/WEEK 68	PLACEBO	138	4.73	0.46	3.5	6.3	138	0.00	0.27	-0.8	1.4
		SB 207499	294	4.77	0.45	3.3	6.8	294	0.01	0.28	-1.0	2.0
	VISIT 21/WEEK 72	PLACEBO	169	4.72	0.43	3.4	6.0	169	0.01	0.30	-0.9	1.2
		SB 207499	351	4.78	0.46	3.5	6.9	350	0.01	0.30	-1.0	2.1
	VISIT 22/WEEK 76	PLACEBO	98	4.73	0.48	3.7	6.4	98	0.03	0.26	-0.7	1.2
		SB 207499	195	4.75	0.50	3.0	7.2	195	-0.00	0.32	-1.1	2.4
	VISIT 23/WEEK 80	PLACEBO	99	4.71	0.51	3.3	6.6	99	0.01	0.29	-0.6	1.1
		SB 207499	188	4.75	0.49	3.2	7.0	188	-0.01	0.33	-0.8	2.2
	VISIT 24/WEEK 84	PLACEBO	161	4.71	0.48	2.8	6.9	161	-0.01	0.36	-2.3	0.9
		SB 207499	332	4.77	0.47	3.0	6.8	331	0.01	0.30	-0.9	2.0
	VISIT 25/WEEK 88	PLACEBO	51	4.68	0.61	3.4	6.8	51	-0.01	0.32	-1.4	0.5
		SB 207499	95	4.73	0.53	3.2	6.5	95	-0.02	0.35	-1.0	1.7
	VISIT 26/WEEK 92	PLACEBO	52	4.61	0.62	3.4	7.2	52	-0.05	0.29	-1.1	0.8
		SB 207499	95	4.73	0.55	3.0	6.8	95	-0.02	0.35	-0.9	2.0
	VISIT 27/WEEK 96	PLACEBO	155	4.70	0.45	3.5	7.1	155	-0.01	0.30	-1.0	0.9
		SB 207499	326	4.73	0.48	3.0	6.9	326	-0.03	0.30	-1.0	2.1
	VISIT 28/WEEK 10	PLACEBO	20	4.57	0.45	3.5	5.5	20	0.06	0.27	-0.5	0.8
		SB 207499	48	4.68	0.41	3.8	5.6	48	-0.02	0.27	-0.5	0.6
	VISIT 29/WEEK 10	PLACEBO	18	4.69	0.34	4.1	5.3	18	0.05	0.20	-0.2	0.4
		SB 207499	39	4.70	0.44	4.0	5.7	39	-0.01	0.27	-0.5	0.5

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Red Blood Cell Count (10 ¹² /L)	VISIT 30/WEEK 10	PLACEBO	128	4.70	0.39	3.7	5.7	128	0.00	0.30	-1.1	0.8
		SB 207499	268	4.73	0.44	3.1	5.9	268	-0.01	0.31	-0.9	1.3
	VISIT 31/WEEK 11	PLACEBO	8	4.74	0.40	4.1	5.3	8	0.15	0.13	0.0	0.3
		SB 207499	17	4.64	0.36	3.8	5.2	17	-0.07	0.42	-1.2	0.7
	VISIT 32/WEEK 11	PLACEBO	9	4.68	0.40	3.9	5.2	9	0.04	0.20	-0.4	0.3
		SB 207499	16	4.78	0.46	4.1	5.8	16	0.00	0.35	-0.7	0.5
	VISIT 33/WEEK 12	PLACEBO	89	4.64	0.43	3.5	5.6	89	-0.05	0.32	-0.9	1.2
		SB 207499	184	4.72	0.42	2.8	5.9	184	0.00	0.30	-1.1	1.1
	VISIT 34/WEEK 12	PLACEBO	3	4.67	0.15	4.5	4.8	3	0.20	0.17	0.1	0.4
		SB 207499	3	4.87	0.15	4.7	5.0	3	0.07	0.40	-0.4	0.3
	VISIT 35/WEEK 12	PLACEBO	3	4.47	0.15	4.3	4.6	3	0.00	0.26	-0.3	0.2
		SB 207499	3	4.70	0.35	4.5	5.1	3	-0.10	0.20	-0.3	0.1
	VISIT 36/WEEK 13	PLACEBO	33	4.65	0.41	3.4	5.5	33	-0.01	0.24	-0.5	0.4
		SB 207499	58	4.74	0.48	2.9	5.7	58	-0.05	0.31	-1.0	0.7
	VISIT 37/WEEK 13	PLACEBO	1	4.60	.	4.6	4.6	1	0.20	.	0.2	0.2
		SB 207499	2	5.05	0.35	4.8	5.3	2	0.55	0.21	0.4	0.7
ENDPOINT		PLACEBO	239	4.70	0.50	2.8	7.1	239	-0.01	0.38	-2.9	1.2
		SB 207499	472	4.72	0.47	2.9	6.9	470	-0.04	0.32	-1.1	2.1

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
White Blood Cell Count ($10^9/L$)	BASELINE	PLACEBO	243	7.73	2.20	3.7	17.9	0	.	.	.	.
		SB 207499	478	7.54	1.95	3.1	17.2	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	236	7.33	1.99	3.7	20.5	236	-0.36	1.78	-8.7	8.7
		SB 207499	468	7.40	2.03	3.5	17.3	466	-0.14	1.69	-7.1	8.6
	VISIT 2/WEEK 1	PLACEBO	234	7.23	1.84	3.7	15.9	234	-0.53	1.74	-10.9	5.3
		SB 207499	450	7.44	2.21	3.8	20.6	448	-0.14	1.84	-6.8	12.2
	VISIT 3/WEEK 2	PLACEBO	219	7.22	1.86	3.5	14.9	219	-0.55	1.79	-9.7	8.9
		SB 207499	452	7.44	2.13	3.9	19.7	451	-0.10	1.77	-6.4	7.0
	VISIT 4/WEEK 4	PLACEBO	213	7.30	1.91	2.1	16.4	213	-0.48	2.02	-8.6	10.4
		SB 207499	445	7.50	2.15	3.8	18.6	444	-0.07	1.84	-7.4	9.6
	VISIT 5/WEEK 8	PLACEBO	205	7.47	2.03	3.6	15.5	205	-0.32	1.93	-9.3	6.2
		SB 207499	437	7.53	2.16	3.7	21.8	436	-0.07	1.94	-11.8	10.4
	VISIT 6/WEEK 12	PLACEBO	204	7.49	2.04	3.4	15.8	204	-0.31	2.22	-11.3	8.7
		SB 207499	429	7.51	2.13	3.3	24.2	428	-0.03	1.77	-7.0	9.2
	VISIT 7/WEEK 16	PLACEBO	195	7.31	1.94	3.3	14.4	195	-0.47	1.86	-9.4	5.1
		SB 207499	421	7.44	2.12	2.9	21.5	420	-0.12	1.72	-6.2	13.0
	VISIT 8/WEEK 20	PLACEBO	194	7.35	1.94	3.8	15.4	194	-0.47	1.81	-9.9	3.6
		SB 207499	423	7.55	2.13	3.4	19.1	422	-0.06	1.91	-8.7	8.8
	VISIT 9/WEEK 24	PLACEBO	187	7.39	1.94	3.8	15.8	187	-0.44	1.81	-9.6	5.7
		SB 207499	422	7.46	2.04	3.4	16.2	421	-0.09	1.71	-8.2	6.1
	VISIT 10/WEEK 28	PLACEBO	185	7.36	1.77	3.8	15.7	185	-0.48	1.89	-9.6	3.1
		SB 207499	413	7.48	2.00	3.6	19.1	412	-0.10	1.70	-8.4	9.1
	VISIT 11/WEEK 32	PLACEBO	185	7.45	2.12	4.0	17.8	185	-0.34	2.04	-10.1	6.6
		SB 207499	410	7.53	2.05	3.2	19.0	409	-0.02	1.70	-7.7	10.2
	VISIT 12/WEEK 36	PLACEBO	181	7.38	2.09	3.6	17.3	181	-0.42	2.05	-9.8	7.5
		SB 207499	408	7.39	1.75	3.3	13.2	407	-0.18	1.61	-6.8	5.3
	VISIT 13/WEEK 40	PLACEBO	179	7.46	1.85	3.9	17.9	179	-0.38	2.05	-10.7	5.5
		SB 207499	398	7.63	2.15	3.4	21.7	397	0.07	1.81	-5.0	16.0
	VISIT 14/WEEK 44	PLACEBO	182	7.65	2.37	3.0	21.8	182	-0.22	2.12	-10.3	6.4
		SB 207499	399	7.54	1.92	3.1	15.0	398	-0.02	1.64	-4.9	8.1

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
White Blood Cell Count ($10^9/L$)	VISIT 15/WEEK 48	PLACEBO	181	7.60	1.97	3.2	17.5	181	-0.21	2.07	-10.3	8.1
		SB 207499	397	7.56	2.05	3.3	17.5	396	-0.02	1.68	-6.0	12.2
	VISIT 16/WEEK 52	PLACEBO	176	7.84	2.75	3.9	30.5	176	-0.04	2.59	-8.0	18.1
		SB 207499	376	7.61	2.01	2.4	15.3	375	0.03	1.76	-5.4	5.9
	VISIT 17/WEEK 56	PLACEBO	166	7.51	2.12	4.0	18.6	166	-0.31	2.09	-8.9	9.2
		SB 207499	356	7.60	2.00	3.4	16.3	356	0.09	1.81	-4.7	7.3
	VISIT 18/WEEK 60	PLACEBO	169	7.46	1.98	3.8	13.5	169	-0.31	2.10	-9.0	6.3
		SB 207499	366	7.63	2.06	3.3	14.6	366	0.10	1.88	-9.3	8.2
	VISIT 19/WEEK 64	PLACEBO	138	7.61	2.26	4.2	23.9	138	-0.33	2.00	-5.3	11.5
		SB 207499	296	7.59	1.98	2.1	16.1	296	0.09	1.67	-5.3	7.1
	VISIT 20/WEEK 68	PLACEBO	138	7.65	2.77	3.5	30.4	138	-0.26	2.55	-7.4	18.0
		SB 207499	294	7.60	2.27	4.1	18.9	294	0.15	1.94	-5.8	8.6
	VISIT 21/WEEK 72	PLACEBO	169	7.60	2.17	3.4	22.0	169	-0.23	2.08	-9.7	9.6
		SB 207499	351	7.62	1.92	3.8	15.0	350	0.10	1.74	-5.9	5.6
	VISIT 22/WEEK 76	PLACEBO	98	7.63	2.20	4.1	15.5	98	-0.06	2.01	-5.7	8.7
		SB 207499	195	7.49	2.14	3.0	15.6	195	0.07	1.74	-5.6	7.2
	VISIT 23/WEEK 80	PLACEBO	99	7.48	1.76	3.3	11.4	99	-0.21	1.75	-6.8	3.8
		SB 207499	188	7.55	2.28	3.6	20.8	188	0.15	1.82	-4.4	9.3
	VISIT 24/WEEK 84	PLACEBO	161	7.61	1.95	3.0	14.6	161	-0.15	2.29	-10.0	7.6
		SB 207499	332	7.62	2.06	3.0	16.5	331	0.13	1.82	-5.8	7.8
	VISIT 25/WEEK 88	PLACEBO	51	7.39	1.71	4.5	15.1	51	-0.48	1.84	-5.6	2.7
		SB 207499	95	7.21	2.26	3.6	19.1	95	-0.24	1.73	-6.0	4.1
	VISIT 26/WEEK 92	PLACEBO	52	7.71	2.17	4.8	15.1	52	-0.10	2.03	-5.7	4.9
		SB 207499	95	7.35	2.05	3.1	14.1	95	-0.09	1.64	-3.9	5.7
	VISIT 27/WEEK 96	PLACEBO	155	7.62	2.10	3.3	17.3	155	-0.22	2.13	-6.3	7.5
		SB 207499	326	7.40	1.89	3.3	16.0	326	-0.06	1.67	-5.6	5.1
	VISIT 28/WEEK 10	PLACEBO	20	7.50	1.97	5.3	14.3	20	-0.85	2.45	-6.7	2.8
		SB 207499	48	7.41	2.35	4.1	17.5	48	-0.07	2.31	-5.3	9.2
	VISIT 29/WEEK 10	PLACEBO	18	7.06	1.07	5.1	9.0	18	-0.99	2.02	-4.7	1.7
		SB 207499	39	7.50	1.92	4.2	12.2	39	-0.02	1.47	-3.6	3.2

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
White Blood Cell Count ($10^9/L$)	VISIT 30/WEEK 10	PLACEBO	128	7.67	1.99	3.5	12.7	128	-0.12	2.20	-8.4	6.9
		SB 207499	268	7.47	2.13	2.7	17.6	268	-0.02	1.70	-5.5	5.1
	VISIT 31/WEEK 11	PLACEBO	8	6.98	1.08	5.0	8.2	8	-1.11	2.18	-5.6	1.1
		SB 207499	17	7.63	1.65	5.1	11.1	17	-0.15	1.11	-2.6	1.4
	VISIT 32/WEEK 11	PLACEBO	9	7.21	1.79	5.2	10.6	9	-1.20	2.64	-5.5	2.5
		SB 207499	16	7.76	1.92	5.8	12.0	16	-0.08	2.32	-3.7	4.2
	VISIT 33/WEEK 12	PLACEBO	89	7.53	2.19	4.0	18.6	89	-0.28	2.05	-5.3	9.2
		SB 207499	184	7.72	2.48	3.3	23.9	184	0.15	2.19	-7.2	16.2
	VISIT 34/WEEK 12	PLACEBO	3	7.00	0.98	6.2	8.1	3	-0.27	0.93	-0.9	0.8
		SB 207499	3	8.23	1.71	7.1	10.2	3	0.03	1.46	-1.3	1.6
	VISIT 35/WEEK 12	PLACEBO	3	12.00	8.31	7.1	21.6	3	4.73	8.29	-0.1	14.3
		SB 207499	3	9.37	2.70	6.7	12.1	3	1.17	2.11	-0.6	3.5
	VISIT 36/WEEK 13	PLACEBO	33	7.36	1.56	4.4	10.6	33	-0.76	1.90	-5.9	1.8
		SB 207499	58	7.86	1.90	3.3	12.2	58	0.08	2.01	-3.8	5.5
	VISIT 37/WEEK 13	PLACEBO	1	7.70	.	7.7	7.7	1	0.40	.	0.4	0.4
		SB 207499	2	7.90	0.71	7.4	8.4	2	1.35	1.77	0.1	2.6
ENDPOINT		PLACEBO	239	7.57	2.26	3.6	22.0	239	-0.19	2.19	-8.4	10.2
		SB 207499	472	7.72	2.24	3.3	23.9	470	0.17	2.05	-8.7	16.2

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Platelets (10 ⁹ /L)	BASELINE	PLACEBO	243	232.64	62.78	118.0	448.0	0	.	.	.	.
		SB 207499	478	241.46	70.56	95.0	638.0	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	236	232.35	64.98	96.0	430.0	236	0.86	43.03	-187.0	144.0
		SB 207499	468	242.07	68.15	91.0	685.0	466	0.09	42.56	-179.0	172.0
	VISIT 2/WEEK 1	PLACEBO	234	228.95	61.34	92.0	449.0	234	-3.43	41.78	-200.0	124.0
		SB 207499	450	244.29	69.95	103.0	671.0	448	3.45	46.15	-169.0	234.0
	VISIT 3/WEEK 2	PLACEBO	219	230.46	62.30	59.0	430.0	219	-0.59	46.45	-181.0	164.0
		SB 207499	452	243.44	67.11	90.0	577.0	451	2.46	43.76	-178.0	216.0
	VISIT 4/WEEK 4	PLACEBO	213	233.19	60.10	83.0	414.0	213	1.78	42.68	-189.0	176.0
		SB 207499	445	244.88	67.60	80.0	632.0	444	4.03	42.26	-164.0	247.0
	VISIT 5/WEEK 8	PLACEBO	205	235.49	67.15	69.0	625.0	205	5.22	51.73	-180.0	298.0
		SB 207499	437	245.72	70.75	97.0	656.0	436	3.09	46.66	-227.0	211.0
	VISIT 6/WEEK 12	PLACEBO	204	237.09	63.93	79.0	582.0	204	4.26	45.40	-197.0	195.0
		SB 207499	429	248.97	68.34	83.0	620.0	428	7.29	45.42	-186.0	203.0
	VISIT 7/WEEK 16	PLACEBO	195	234.73	61.57	98.0	462.0	195	3.35	44.24	-172.0	144.0
		SB 207499	420	246.68	66.41	108.0	686.0	419	4.82	43.80	-256.0	152.0
	VISIT 8/WEEK 20	PLACEBO	194	240.45	66.27	96.0	629.0	194	9.08	48.52	-183.0	336.0
		SB 207499	423	248.53	69.71	87.0	732.0	422	6.58	45.09	-161.0	242.0
	VISIT 9/WEEK 24	PLACEBO	187	237.65	61.03	94.0	429.0	187	6.27	43.23	-200.0	182.0
		SB 207499	422	244.75	65.42	111.0	632.0	421	3.95	43.03	-179.0	224.0
	VISIT 10/WEEK 28	PLACEBO	185	239.28	70.19	102.0	663.0	185	7.27	47.98	-149.0	293.0
		SB 207499	413	245.93	68.39	110.0	588.0	412	5.43	47.51	-184.0	265.0
	VISIT 11/WEEK 32	PLACEBO	185	234.20	60.71	89.0	489.0	185	2.24	41.62	-180.0	144.0
		SB 207499	410	246.60	68.39	79.0	578.0	409	5.45	47.30	-160.0	248.0
	VISIT 12/WEEK 36	PLACEBO	181	236.87	63.96	81.0	415.0	181	4.78	47.03	-156.0	202.0
		SB 207499	408	246.07	64.19	118.0	559.0	407	5.08	43.58	-187.0	143.0
	VISIT 13/WEEK 40	PLACEBO	179	240.51	70.77	102.0	738.0	179	5.78	54.35	-171.0	428.0
		SB 207499	398	245.98	65.83	116.0	570.0	397	4.62	47.84	-183.0	264.0
	VISIT 14/WEEK 44	PLACEBO	182	236.88	64.61	90.0	574.0	182	2.94	48.22	-177.0	264.0
		SB 207499	399	246.08	65.21	111.0	576.0	398	4.90	48.04	-184.0	321.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Platelets (10 ⁹ /L)	VISIT 15/WEEK 48	PLACEBO	181	238.59	74.08	95.0	790.0	181	5.48	60.56	-162.0	497.0
		SB 207499	397	245.90	66.25	46.0	518.0	396	5.44	50.98	-207.0	366.0
	VISIT 16/WEEK 52	PLACEBO	176	239.71	67.88	91.0	491.0	176	4.68	54.59	-184.0	237.0
		SB 207499	376	245.82	64.80	98.0	595.0	375	3.98	47.84	-218.0	225.0
	VISIT 17/WEEK 56	PLACEBO	166	239.10	74.84	87.0	731.0	166	8.81	61.56	-205.0	438.0
		SB 207499	356	248.51	67.46	43.0	503.0	356	7.13	48.20	-232.0	201.0
	VISIT 18/WEEK 60	PLACEBO	169	247.18	77.94	85.0	608.0	169	12.98	57.82	-189.0	352.0
		SB 207499	366	250.34	65.76	129.0	606.0	366	8.29	46.19	-270.0	229.0
	VISIT 19/WEEK 64	PLACEBO	138	249.43	64.52	105.0	457.0	138	14.48	45.87	-130.0	160.0
		SB 207499	296	252.13	69.07	98.0	631.0	296	12.40	48.41	-221.0	220.0
	VISIT 20/WEEK 68	PLACEBO	138	251.55	76.95	120.0	587.0	138	17.39	58.80	-200.0	271.0
		SB 207499	293	253.42	71.06	114.0	659.0	293	11.87	54.82	-305.0	353.0
	VISIT 21/WEEK 72	PLACEBO	169	257.40	70.39	109.0	606.0	169	23.27	53.81	-182.0	296.0
		SB 207499	351	254.65	70.08	80.0	671.0	350	12.82	52.68	-336.0	418.0
	VISIT 22/WEEK 76	PLACEBO	98	240.57	61.22	102.0	440.0	98	15.41	47.12	-178.0	212.0
		SB 207499	195	255.88	68.36	122.0	482.0	195	11.89	51.49	-269.0	174.0
	VISIT 23/WEEK 80	PLACEBO	99	242.24	63.34	107.0	430.0	99	15.86	47.02	-153.0	175.0
		SB 207499	188	255.16	68.67	136.0	619.0	188	13.49	55.52	-284.0	341.0
	VISIT 24/WEEK 84	PLACEBO	161	248.93	64.82	103.0	506.0	161	13.28	50.08	-177.0	230.0
		SB 207499	332	255.96	68.99	108.0	499.0	331	14.06	52.71	-296.0	236.0
	VISIT 25/WEEK 88	PLACEBO	51	247.59	75.08	110.0	483.0	51	25.20	50.72	-79.0	210.0
		SB 207499	95	246.45	71.82	113.0	468.0	95	7.03	67.62	-343.0	163.0
	VISIT 26/WEEK 92	PLACEBO	52	245.67	74.00	141.0	522.0	52	24.73	54.80	-148.0	212.0
		SB 207499	95	247.67	78.83	106.0	505.0	95	6.41	61.62	-344.0	162.0
	VISIT 27/WEEK 96	PLACEBO	155	255.06	74.67	82.0	745.0	155	21.49	55.21	-126.0	435.0
		SB 207499	326	256.13	69.15	102.0	564.0	326	15.44	53.81	-355.0	287.0
	VISIT 28/WEEK 10	PLACEBO	20	234.45	88.04	95.0	415.0	20	20.95	50.42	-61.0	159.0
		SB 207499	48	239.71	58.88	145.0	424.0	48	-0.38	48.62	-172.0	154.0
	VISIT 29/WEEK 10	PLACEBO	18	231.06	60.37	152.0	376.0	18	21.44	33.02	-57.0	90.0
		SB 207499	39	238.64	62.98	138.0	471.0	39	8.31	37.58	-101.0	83.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Platelets (10 ⁹ /L)	VISIT 30/WEEK 10	PLACEBO	128	257.77	75.54	100.0	521.0	128	22.70	55.63	-142.0	280.0
		SB 207499	268	255.19	65.08	128.0	565.0	268	15.38	48.07	-163.0	169.0
	VISIT 31/WEEK 11	PLACEBO	8	210.25	32.10	167.0	263.0	8	5.25	23.46	-43.0	27.0
		SB 207499	17	244.47	57.98	170.0	361.0	17	9.94	33.16	-50.0	109.0
	VISIT 32/WEEK 11	PLACEBO	9	218.67	26.41	162.0	259.0	9	19.78	38.32	-40.0	86.0
		SB 207499	16	251.00	67.86	166.0	397.0	16	13.81	20.01	-38.0	50.0
	VISIT 33/WEEK 12	PLACEBO	89	252.54	57.03	121.0	427.0	89	20.38	39.33	-95.0	104.0
		SB 207499	184	259.23	72.79	102.0	521.0	184	19.88	53.19	-151.0	219.0
	VISIT 34/WEEK 12	PLACEBO	3	197.00	49.00	158.0	252.0	3	-6.67	36.77	-47.0	25.0
		SB 207499	3	264.00	51.45	221.0	321.0	3	37.67	31.77	1.0	57.0
	VISIT 35/WEEK 12	PLACEBO	3	249.33	30.17	229.0	284.0	3	45.67	71.39	1.0	128.0
		SB 207499	3	276.00	57.71	235.0	342.0	3	49.67	24.95	31.0	78.0
	VISIT 36/WEEK 13	PLACEBO	33	249.27	53.31	138.0	392.0	33	26.21	43.24	-56.0	126.0
		SB 207499	58	262.02	72.38	137.0	544.0	58	26.57	57.89	-150.0	192.0
	VISIT 37/WEEK 13	PLACEBO	1	259.00	.	259.0	259.0	1	32.00	.	32.0	32.0
		SB 207499	2	236.50	23.33	220.0	253.0	2	29.00	5.66	25.0	33.0
	ENDPOINT	PLACEBO	239	250.25	75.11	81.0	745.0	239	17.92	57.86	-177.0	435.0
		SB 207499	472	262.17	76.93	102.0	671.0	470	20.46	55.71	-355.0	248.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Basophils Absolute (10 ⁹ /L)	BASELINE	PLACEBO	243	0.03	0.02	0.0	0.1	0	.	.	.	.
		SB 207499	478	0.03	0.02	0.0	0.1	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	234	0.02	0.02	0.0	0.1	234	-0.00	0.02	-0.0	0.1
		SB 207499	460	0.02	0.02	0.0	0.2	458	-0.00	0.02	-0.1	0.2
	VISIT 2/WEEK 1	PLACEBO	229	0.03	0.02	0.0	0.1	229	-0.00	0.02	-0.1	0.1
		SB 207499	446	0.03	0.02	0.0	0.1	444	0.00	0.02	-0.1	0.1
	VISIT 3/WEEK 2	PLACEBO	218	0.02	0.02	0.0	0.1	218	-0.00	0.02	-0.1	0.1
		SB 207499	449	0.02	0.02	0.0	0.1	448	-0.00	0.02	-0.1	0.1
	VISIT 4/WEEK 4	PLACEBO	212	0.02	0.02	0.0	0.1	212	-0.00	0.02	-0.1	0.1
		SB 207499	443	0.03	0.02	0.0	0.2	442	-0.00	0.02	-0.1	0.2
	VISIT 5/WEEK 8	PLACEBO	203	0.02	0.02	0.0	0.1	203	-0.00	0.02	-0.1	0.1
		SB 207499	431	0.03	0.02	0.0	0.1	430	-0.00	0.02	-0.1	0.1
	VISIT 6/WEEK 12	PLACEBO	201	0.02	0.02	0.0	0.1	201	-0.00	0.02	-0.1	0.1
		SB 207499	426	0.03	0.02	0.0	0.1	425	-0.00	0.02	-0.1	0.1
	VISIT 7/WEEK 16	PLACEBO	195	0.02	0.02	0.0	0.1	195	-0.00	0.02	-0.1	0.1
		SB 207499	417	0.02	0.02	0.0	0.1	416	-0.00	0.02	-0.1	0.1
	VISIT 8/WEEK 20	PLACEBO	193	0.02	0.02	0.0	0.1	193	-0.00	0.02	-0.1	0.1
		SB 207499	419	0.03	0.02	0.0	0.2	418	-0.00	0.02	-0.1	0.1
	VISIT 9/WEEK 24	PLACEBO	187	0.03	0.02	0.0	0.1	187	0.00	0.02	-0.1	0.1
		SB 207499	419	0.03	0.07	0.0	1.4	418	0.00	0.07	-0.1	1.4
	VISIT 10/WEEK 28	PLACEBO	184	0.02	0.02	0.0	0.1	184	-0.00	0.02	-0.1	0.1
		SB 207499	412	0.03	0.02	0.0	0.1	411	-0.00	0.02	-0.1	0.1
	VISIT 11/WEEK 32	PLACEBO	184	0.03	0.02	0.0	0.2	184	0.00	0.02	-0.1	0.1
		SB 207499	408	0.03	0.02	0.0	0.1	407	-0.00	0.02	-0.1	0.1
	VISIT 12/WEEK 36	PLACEBO	181	0.02	0.01	0.0	0.1	181	-0.00	0.02	-0.1	0.1
		SB 207499	407	0.03	0.02	0.0	0.2	406	0.00	0.02	-0.1	0.1
	VISIT 13/WEEK 40	PLACEBO	177	0.03	0.01	0.0	0.1	177	-0.00	0.02	-0.0	0.1
		SB 207499	398	0.03	0.02	0.0	0.2	397	0.00	0.02	-0.1	0.2
	VISIT 14/WEEK 44	PLACEBO	181	0.03	0.02	0.0	0.2	181	0.00	0.02	-0.1	0.2
		SB 207499	397	0.03	0.02	0.0	0.1	396	0.00	0.02	-0.1	0.1

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Basophils Absolute (10 ⁹ /L)	VISIT 15/WEEK 48	PLACEBO	180	0.03	0.02	0.0	0.2	180	0.00	0.02	-0.1	0.1
		SB 207499	396	0.03	0.02	0.0	0.3	395	-0.00	0.02	-0.1	0.3
	VISIT 16/WEEK 52	PLACEBO	176	0.02	0.02	0.0	0.1	176	-0.00	0.02	-0.1	0.1
		SB 207499	375	0.03	0.01	0.0	0.1	374	-0.00	0.02	-0.1	0.1
	VISIT 17/WEEK 56	PLACEBO	165	0.02	0.02	0.0	0.1	165	-0.00	0.02	-0.1	0.1
		SB 207499	355	0.02	0.01	0.0	0.1	355	-0.00	0.02	-0.1	0.1
	VISIT 18/WEEK 60	PLACEBO	165	0.03	0.02	0.0	0.2	165	-0.00	0.02	-0.1	0.2
		SB 207499	365	0.02	0.02	0.0	0.2	365	-0.00	0.02	-0.1	0.1
	VISIT 19/WEEK 64	PLACEBO	138	0.03	0.02	0.0	0.1	138	-0.00	0.02	-0.1	0.1
		SB 207499	295	0.02	0.02	0.0	0.2	295	-0.00	0.02	-0.1	0.1
	VISIT 20/WEEK 68	PLACEBO	137	0.02	0.02	0.0	0.1	137	-0.00	0.02	-0.1	0.1
		SB 207499	294	0.02	0.02	0.0	0.1	294	-0.00	0.02	-0.1	0.1
	VISIT 21/WEEK 72	PLACEBO	167	0.02	0.01	0.0	0.1	167	-0.00	0.02	-0.0	0.1
		SB 207499	350	0.02	0.01	0.0	0.1	349	-0.00	0.02	-0.1	0.1
	VISIT 22/WEEK 76	PLACEBO	95	0.02	0.01	0.0	0.1	95	-0.00	0.02	-0.0	0.0
		SB 207499	195	0.02	0.02	0.0	0.1	195	-0.00	0.02	-0.1	0.1
	VISIT 23/WEEK 80	PLACEBO	98	0.03	0.02	0.0	0.1	98	-0.00	0.02	-0.0	0.1
		SB 207499	187	0.02	0.02	0.0	0.1	187	-0.00	0.02	-0.1	0.1
	VISIT 24/WEEK 84	PLACEBO	161	0.02	0.01	0.0	0.1	161	-0.00	0.02	-0.0	0.0
		SB 207499	331	0.03	0.02	0.0	0.2	330	-0.00	0.02	-0.1	0.1
	VISIT 25/WEEK 88	PLACEBO	51	0.02	0.01	0.0	0.1	51	-0.00	0.02	-0.0	0.0
		SB 207499	95	0.02	0.01	0.0	0.1	95	-0.00	0.02	-0.1	0.1
	VISIT 26/WEEK 92	PLACEBO	51	0.02	0.01	0.0	0.1	51	-0.01	0.02	-0.0	0.0
		SB 207499	95	0.03	0.01	0.0	0.1	95	0.00	0.02	-0.1	0.1
	VISIT 27/WEEK 96	PLACEBO	155	0.02	0.02	0.0	0.1	155	-0.00	0.02	-0.1	0.1
		SB 207499	324	0.03	0.02	0.0	0.1	324	-0.00	0.02	-0.1	0.1
	VISIT 28/WEEK 10	PLACEBO	20	0.02	0.01	0.0	0.1	20	-0.00	0.02	-0.0	0.0
		SB 207499	48	0.03	0.02	0.0	0.1	48	0.00	0.02	-0.0	0.1
	VISIT 29/WEEK 10	PLACEBO	18	0.02	0.01	0.0	0.0	18	-0.01	0.02	-0.1	0.0
		SB 207499	39	0.03	0.02	0.0	0.1	39	0.00	0.02	-0.0	0.1

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Basophils Absolute (10 ⁹ /L)	VISIT 30/WEEK 10	PLACEBO	128	0.02	0.02	0.0	0.1	128	-0.00	0.02	-0.1	0.1
		SB 207499	265	0.02	0.02	0.0	0.1	265	-0.00	0.02	-0.1	0.1
	VISIT 31/WEEK 11	PLACEBO	8	0.02	0.01	0.0	0.0	8	-0.01	0.03	-0.1	0.0
		SB 207499	17	0.03	0.01	0.0	0.1	17	0.00	0.02	-0.0	0.0
	VISIT 32/WEEK 11	PLACEBO	9	0.03	0.01	0.0	0.1	9	-0.00	0.02	-0.0	0.0
		SB 207499	16	0.02	0.01	0.0	0.0	16	-0.01	0.01	-0.0	0.0
	VISIT 33/WEEK 12	PLACEBO	87	0.02	0.02	0.0	0.1	87	-0.00	0.02	-0.0	0.1
		SB 207499	184	0.02	0.02	0.0	0.2	184	-0.00	0.02	-0.1	0.1
	VISIT 34/WEEK 12	PLACEBO	3	0.01	0.01	0.0	0.0	3	-0.02	0.03	-0.1	0.0
		SB 207499	3	0.02	0.02	0.0	0.0	3	0.00	0.03	-0.0	0.0
	VISIT 35/WEEK 12	PLACEBO	3	0.03	0.03	0.0	0.1	3	-0.00	0.01	-0.0	0.0
		SB 207499	3	0.01	0.01	0.0	0.0	3	-0.00	0.02	-0.0	0.0
	VISIT 36/WEEK 13	PLACEBO	33	0.02	0.01	0.0	0.1	33	-0.01	0.02	-0.1	0.0
		SB 207499	58	0.02	0.01	0.0	0.1	58	-0.01	0.02	-0.0	0.0
	VISIT 37/WEEK 13	PLACEBO	1	0.02	.	0.0	0.0	1	-0.05	.	-0.1	-0.1
		SB 207499	2	0.02	0.01	0.0	0.0	2	0.00	0.00	0.0	0.0
ENDPOINT		PLACEBO	239	0.02	0.02	0.0	0.1	239	-0.00	0.02	-0.1	0.1
		SB 207499	472	0.02	0.02	0.0	0.2	470	-0.00	0.02	-0.1	0.1

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Eosinophils Absolute (10 ⁹ /L)	BASELINE	PLACEBO	243	0.25	0.22	0.0	2.3	0	.	.	.	.
		SB 207499	478	0.22	0.15	0.0	1.0	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	234	0.24	0.18	0.0	1.1	234	-0.01	0.20	-1.5	1.0
		SB 207499	460	0.21	0.15	0.0	1.1	458	-0.01	0.13	-0.7	0.6
	VISIT 2/WEEK 1	PLACEBO	229	0.24	0.30	0.0	3.4	229	-0.01	0.19	-0.6	1.5
		SB 207499	446	0.21	0.15	0.0	1.2	444	-0.01	0.14	-0.8	0.8
	VISIT 3/WEEK 2	PLACEBO	218	0.24	0.23	0.0	2.3	218	-0.01	0.20	-0.9	1.2
		SB 207499	449	0.20	0.15	0.0	1.0	448	-0.01	0.14	-0.7	0.8
	VISIT 4/WEEK 4	PLACEBO	212	0.23	0.20	0.0	1.6	212	-0.02	0.17	-0.7	0.5
		SB 207499	443	0.21	0.14	0.0	0.9	442	-0.02	0.14	-0.5	0.8
	VISIT 5/WEEK 8	PLACEBO	203	0.24	0.28	0.0	3.2	203	-0.01	0.20	-0.8	1.3
		SB 207499	431	0.20	0.14	0.0	0.9	430	-0.01	0.14	-0.6	0.7
	VISIT 6/WEEK 12	PLACEBO	201	0.21	0.19	0.0	1.8	201	-0.04	0.17	-0.8	0.5
		SB 207499	426	0.19	0.14	0.0	0.9	425	-0.02	0.13	-0.6	0.5
	VISIT 7/WEEK 16	PLACEBO	195	0.21	0.18	0.0	2.0	195	-0.04	0.21	-2.0	0.8
		SB 207499	417	0.20	0.15	0.0	0.9	416	-0.02	0.14	-0.6	0.8
	VISIT 8/WEEK 20	PLACEBO	193	0.21	0.16	0.0	1.1	193	-0.04	0.20	-2.0	0.5
		SB 207499	419	0.20	0.13	0.0	0.9	418	-0.02	0.14	-0.6	0.5
	VISIT 9/WEEK 24	PLACEBO	187	0.21	0.25	0.0	3.1	187	-0.03	0.25	-2.0	2.0
		SB 207499	419	0.21	0.15	0.0	1.6	418	-0.01	0.14	-0.5	1.4
	VISIT 10/WEEK 28	PLACEBO	184	0.22	0.22	0.0	2.4	184	-0.03	0.22	-1.5	1.3
		SB 207499	412	0.21	0.16	0.0	1.0	411	-0.01	0.13	-0.6	0.6
	VISIT 11/WEEK 32	PLACEBO	184	0.23	0.25	0.0	2.6	184	-0.02	0.21	-1.1	1.5
		SB 207499	408	0.21	0.14	0.0	1.0	407	-0.01	0.15	-0.7	0.9
	VISIT 12/WEEK 36	PLACEBO	181	0.23	0.25	0.0	2.8	181	-0.03	0.21	-1.0	1.7
		SB 207499	407	0.21	0.15	0.0	1.1	406	-0.01	0.15	-0.6	0.9
	VISIT 13/WEEK 40	PLACEBO	177	0.23	0.21	0.0	2.1	177	-0.02	0.19	-1.4	1.0
		SB 207499	398	0.22	0.16	0.0	1.1	397	-0.00	0.16	-0.8	1.0
	VISIT 14/WEEK 44	PLACEBO	181	0.26	0.42	0.0	5.2	181	0.01	0.35	-0.8	4.1
		SB 207499	397	0.22	0.14	0.0	1.0	396	-0.01	0.13	-0.6	0.7

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Eosinophils Absolute (10 ⁹ /L)	VISIT 15/WEEK 48	PLACEBO	180	0.24	0.38	0.0	4.9	180	-0.00	0.32	-0.7	3.8
		SB 207499	396	0.21	0.16	0.0	0.9	395	-0.01	0.15	-0.6	0.8
	VISIT 16/WEEK 52	PLACEBO	176	0.23	0.25	0.0	2.4	176	-0.02	0.19	-0.8	1.2
		SB 207499	375	0.22	0.15	0.0	1.1	374	-0.00	0.15	-0.8	0.9
	VISIT 17/WEEK 56	PLACEBO	165	0.22	0.20	0.0	1.7	165	-0.02	0.16	-1.0	0.6
		SB 207499	355	0.22	0.16	0.0	1.2	355	-0.00	0.15	-0.8	0.9
	VISIT 18/WEEK 60	PLACEBO	165	0.22	0.22	0.0	1.9	165	-0.03	0.15	-0.5	0.6
		SB 207499	365	0.21	0.17	0.0	1.7	365	-0.01	0.15	-0.6	1.2
	VISIT 19/WEEK 64	PLACEBO	138	0.22	0.27	0.0	2.9	138	-0.03	0.22	-1.3	1.8
		SB 207499	295	0.21	0.15	0.0	1.0	295	-0.00	0.15	-0.8	0.9
	VISIT 20/WEEK 68	PLACEBO	137	0.22	0.28	0.0	2.9	137	-0.03	0.22	-1.1	1.8
		SB 207499	294	0.21	0.19	0.0	2.2	294	-0.01	0.16	-0.7	1.7
	VISIT 21/WEEK 72	PLACEBO	167	0.23	0.30	0.0	3.5	167	-0.02	0.26	-1.3	2.3
		SB 207499	350	0.22	0.16	0.0	0.9	349	-0.00	0.15	-0.6	0.8
	VISIT 22/WEEK 76	PLACEBO	95	0.22	0.18	0.0	1.3	95	-0.01	0.12	-0.4	0.4
		SB 207499	195	0.21	0.15	0.0	0.8	195	-0.02	0.13	-0.6	0.4
	VISIT 23/WEEK 80	PLACEBO	98	0.22	0.22	0.0	2.0	98	-0.01	0.15	-0.3	0.9
		SB 207499	187	0.20	0.14	0.0	0.7	187	-0.02	0.14	-0.6	0.3
	VISIT 24/WEEK 84	PLACEBO	161	0.23	0.20	0.0	1.6	161	-0.02	0.16	-0.8	0.5
		SB 207499	331	0.20	0.14	0.0	1.0	330	-0.02	0.13	-0.6	0.5
	VISIT 25/WEEK 88	PLACEBO	51	0.20	0.13	0.0	0.6	51	-0.02	0.16	-0.7	0.4
		SB 207499	95	0.20	0.11	0.0	0.6	95	-0.01	0.14	-0.6	0.3
	VISIT 26/WEEK 92	PLACEBO	51	0.21	0.15	0.0	0.9	51	-0.01	0.12	-0.5	0.2
		SB 207499	95	0.20	0.13	0.0	0.8	95	-0.01	0.16	-0.6	0.7
	VISIT 27/WEEK 96	PLACEBO	155	0.24	0.18	0.0	1.3	155	-0.01	0.21	-1.4	1.1
		SB 207499	324	0.21	0.14	0.0	0.8	324	-0.01	0.14	-0.6	0.5
	VISIT 28/WEEK 10	PLACEBO	20	0.20	0.12	0.0	0.5	20	-0.00	0.13	-0.3	0.3
		SB 207499	48	0.19	0.10	0.0	0.4	48	-0.01	0.13	-0.6	0.2
	VISIT 29/WEEK 10	PLACEBO	18	0.23	0.14	0.0	0.6	18	0.01	0.11	-0.2	0.2
		SB 207499	39	0.19	0.11	0.1	0.5	39	0.00	0.14	-0.6	0.3

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Eosinophils Absolute (10 ⁹ /L)	VISIT 30/WEEK 10	PLACEBO	128	0.23	0.15	0.0	0.9	128	-0.03	0.26	-2.3	0.9
		SB 207499	265	0.22	0.15	0.0	1.1	265	0.00	0.16	-0.8	0.9
	VISIT 31/WEEK 11	PLACEBO	8	0.22	0.15	0.1	0.5	8	0.02	0.12	-0.2	0.2
		SB 207499	17	0.19	0.08	0.1	0.3	17	-0.01	0.15	-0.5	0.2
	VISIT 32/WEEK 11	PLACEBO	9	0.17	0.12	0.0	0.4	9	-0.03	0.09	-0.2	0.1
		SB 207499	16	0.17	0.08	0.0	0.3	16	-0.03	0.14	-0.5	0.1
	VISIT 33/WEEK 12	PLACEBO	87	0.20	0.15	0.0	0.8	87	-0.05	0.23	-1.9	0.3
		SB 207499	184	0.20	0.12	0.0	0.8	184	-0.01	0.16	-0.8	0.5
	VISIT 34/WEEK 12	PLACEBO	3	0.07	0.04	0.0	0.1	3	-0.03	0.10	-0.1	0.1
		SB 207499	3	0.15	0.07	0.1	0.2	3	-0.07	0.10	-0.2	0.0
	VISIT 35/WEEK 12	PLACEBO	3	0.07	0.03	0.0	0.1	3	-0.03	0.10	-0.1	0.1
		SB 207499	3	0.13	0.07	0.1	0.2	3	-0.09	0.03	-0.1	-0.1
	VISIT 36/WEEK 13	PLACEBO	33	0.22	0.24	0.0	1.4	33	-0.06	0.18	-0.9	0.2
		SB 207499	58	0.21	0.15	0.0	0.6	58	-0.00	0.13	-0.5	0.4
	VISIT 37/WEEK 13	PLACEBO	1	0.08	.	0.1	0.1	1	0.06	.	0.1	0.1
		SB 207499	2	0.17	0.06	0.1	0.2	2	-0.04	0.05	-0.1	0.0
ENDPOINT		PLACEBO	239	0.21	0.18	0.0	1.4	239	-0.04	0.18	-0.9	0.9
		SB 207499	472	0.20	0.15	0.0	1.1	470	-0.02	0.15	-0.7	0.7

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Lymphocytes Absolute (10 ⁹ /L)	BASELINE	PLACEBO	243	2.08	0.76	0.6	6.5	0	.	.	.	.
		SB 207499	478	2.10	0.66	0.6	5.1	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	234	2.02	0.77	0.6	6.8	234	-0.05	0.56	-2.4	1.9
		SB 207499	460	2.06	0.71	0.4	7.1	458	-0.05	0.50	-1.8	2.6
	VISIT 2/WEEK 1	PLACEBO	229	2.06	0.82	0.6	8.5	229	-0.02	0.52	-1.9	2.0
		SB 207499	446	2.03	0.68	0.6	6.8	444	-0.08	0.51	-1.8	2.2
	VISIT 3/WEEK 2	PLACEBO	218	2.07	0.82	0.6	7.5	218	-0.03	0.55	-2.6	1.5
		SB 207499	449	2.04	0.71	0.5	6.9	448	-0.06	0.48	-2.3	1.8
	VISIT 4/WEEK 4	PLACEBO	212	2.05	0.78	0.5	6.4	212	-0.05	0.54	-1.9	2.0
		SB 207499	443	2.10	0.76	0.8	7.6	442	-0.00	0.58	-2.1	3.6
	VISIT 5/WEEK 8	PLACEBO	203	2.02	0.85	0.6	7.4	203	-0.07	0.58	-2.7	2.4
		SB 207499	431	2.04	0.78	0.8	8.4	430	-0.06	0.56	-1.7	3.7
	VISIT 6/WEEK 12	PLACEBO	201	1.97	0.81	0.5	8.7	201	-0.09	0.55	-2.4	2.2
		SB 207499	426	2.06	0.75	0.3	6.9	425	-0.04	0.55	-2.4	2.8
	VISIT 7/WEEK 16	PLACEBO	195	1.99	0.90	0.5	9.6	195	-0.09	0.53	-1.7	3.0
		SB 207499	417	1.99	0.70	0.5	6.2	416	-0.12	0.49	-1.7	2.7
	VISIT 8/WEEK 20	PLACEBO	193	1.98	0.77	0.6	7.1	193	-0.11	0.51	-2.6	1.6
		SB 207499	419	2.01	0.83	0.5	10.6	418	-0.10	0.60	-1.7	5.4
	VISIT 9/WEEK 24	PLACEBO	187	1.98	0.79	0.6	8.0	187	-0.10	0.53	-2.4	1.5
		SB 207499	419	2.02	0.75	0.1	9.5	418	-0.09	0.53	-1.5	4.4
	VISIT 10/WEEK 28	PLACEBO	184	2.04	0.81	0.6	8.6	184	-0.04	0.56	-2.3	2.1
		SB 207499	412	2.02	0.68	0.6	5.5	411	-0.09	0.50	-1.9	2.4
	VISIT 11/WEEK 32	PLACEBO	184	2.02	0.91	0.6	10.7	184	-0.04	0.56	-2.2	4.2
		SB 207499	408	2.04	0.66	0.6	5.6	407	-0.06	0.51	-2.2	2.0
	VISIT 12/WEEK 36	PLACEBO	181	2.04	0.93	0.8	10.9	181	-0.04	0.61	-1.6	4.4
		SB 207499	407	2.05	0.65	0.7	4.9	406	-0.06	0.48	-2.1	1.8
	VISIT 13/WEEK 40	PLACEBO	177	2.09	1.02	0.7	11.8	177	-0.01	0.66	-2.0	5.3
		SB 207499	398	2.06	0.68	0.7	6.7	397	-0.04	0.51	-1.9	1.6
	VISIT 14/WEEK 44	PLACEBO	181	2.13	1.12	0.5	12.5	181	0.03	0.73	-1.8	5.9
		SB 207499	397	2.07	0.68	0.6	4.6	396	-0.04	0.49	-2.2	2.1

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Lymphocytes Absolute (10 ⁹ /L)	VISIT 15/WEEK 48	PLACEBO	180	2.12	1.02	0.6	12.0	180	0.03	0.67	-1.7	5.5
		SB 207499	396	2.08	0.74	0.8	7.8	395	-0.02	0.54	-1.9	2.7
	VISIT 16/WEEK 52	PLACEBO	176	2.11	1.44	0.6	18.8	176	0.02	1.08	-2.0	12.3
		SB 207499	375	2.09	0.70	0.5	4.7	374	-0.01	0.52	-1.7	1.6
	VISIT 17/WEEK 56	PLACEBO	165	2.05	1.00	0.6	11.2	165	-0.03	0.61	-1.6	4.7
		SB 207499	355	2.08	0.69	0.8	8.0	355	-0.01	0.52	-2.5	2.9
	VISIT 18/WEEK 60	PLACEBO	165	2.04	0.71	0.8	4.9	165	-0.01	0.51	-1.7	1.6
		SB 207499	365	2.06	0.78	0.5	8.6	365	-0.04	0.59	-2.0	4.2
	VISIT 19/WEEK 64	PLACEBO	138	2.11	1.27	0.7	14.2	138	-0.01	0.83	-1.5	7.6
		SB 207499	295	2.05	0.69	0.9	4.8	295	-0.01	0.52	-1.4	2.0
	VISIT 20/WEEK 68	PLACEBO	137	2.19	1.76	0.7	20.7	137	0.09	1.32	-1.5	14.2
		SB 207499	294	2.08	0.78	0.7	7.2	294	0.01	0.51	-1.4	2.1
	VISIT 21/WEEK 72	PLACEBO	167	2.08	1.10	0.6	13.1	167	-0.00	0.73	-1.5	6.6
		SB 207499	350	2.11	0.71	0.7	4.9	349	0.01	0.54	-2.1	1.8
	VISIT 22/WEEK 76	PLACEBO	95	2.13	0.82	0.9	5.3	95	0.06	0.65	-1.8	2.7
		SB 207499	195	2.00	0.72	0.7	5.3	195	-0.07	0.46	-2.1	1.3
	VISIT 23/WEEK 80	PLACEBO	98	2.03	0.76	0.9	4.9	98	-0.02	0.58	-2.0	1.6
		SB 207499	187	2.07	0.85	0.8	9.0	187	-0.02	0.57	-1.7	3.9
	VISIT 24/WEEK 84	PLACEBO	161	2.09	0.72	0.5	4.5	161	0.05	0.60	-1.8	2.7
		SB 207499	331	2.09	0.73	0.7	7.7	330	-0.01	0.55	-2.3	2.5
	VISIT 25/WEEK 88	PLACEBO	51	2.02	0.65	0.6	3.9	51	-0.03	0.63	-2.6	1.4
		SB 207499	95	1.98	0.67	0.9	4.5	95	-0.08	0.50	-2.0	1.3
	VISIT 26/WEEK 92	PLACEBO	51	2.00	0.74	0.6	4.3	51	-0.02	0.59	-1.7	1.8
		SB 207499	95	1.96	0.59	0.9	4.2	95	-0.10	0.47	-1.2	2.3
	VISIT 27/WEEK 96	PLACEBO	155	2.03	0.72	0.5	4.4	155	-0.03	0.54	-1.7	1.4
		SB 207499	324	2.01	0.75	0.7	9.4	324	-0.08	0.57	-2.4	4.2
	VISIT 28/WEEK 10	PLACEBO	20	2.14	0.69	0.8	3.5	20	0.07	0.55	-0.9	0.9
		SB 207499	48	1.99	0.62	1.1	3.8	48	-0.05	0.51	-1.3	1.3
	VISIT 29/WEEK 10	PLACEBO	18	2.11	0.71	1.1	3.2	18	0.10	0.48	-0.8	0.9
		SB 207499	39	1.94	0.57	0.8	3.1	39	-0.12	0.53	-1.4	1.1

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Lymphocytes Absolute (10 ⁹ /L)	VISIT 30/WEEK 10	PLACEBO	128	1.99	0.72	0.8	4.0	128	-0.07	0.54	-1.5	1.5
		SB 207499	265	1.97	0.62	0.6	3.8	265	-0.12	0.49	-2.0	1.5
	VISIT 31/WEEK 11	PLACEBO	8	2.09	0.67	1.3	3.1	8	-0.02	0.65	-1.0	0.8
		SB 207499	17	2.15	0.55	1.4	3.1	17	-0.00	0.42	-1.0	0.6
	VISIT 32/WEEK 11	PLACEBO	9	2.01	0.76	0.9	3.3	9	-0.07	0.68	-1.0	0.7
		SB 207499	16	1.89	0.58	1.0	3.0	16	-0.21	0.53	-1.3	0.5
	VISIT 33/WEEK 12	PLACEBO	87	1.86	0.62	0.7	4.0	87	-0.21	0.47	-1.9	0.7
		SB 207499	184	1.90	0.61	0.8	3.6	184	-0.14	0.50	-2.0	1.6
	VISIT 34/WEEK 12	PLACEBO	3	1.89	0.55	1.3	2.4	3	-0.29	0.20	-0.5	-0.1
		SB 207499	3	1.78	0.31	1.4	2.1	3	-0.17	0.48	-0.6	0.3
	VISIT 35/WEEK 12	PLACEBO	3	2.04	0.54	1.6	2.6	3	-0.15	0.45	-0.7	0.2
		SB 207499	3	1.67	0.15	1.5	1.8	3	-0.28	0.35	-0.5	0.1
	VISIT 36/WEEK 13	PLACEBO	33	2.04	0.66	1.1	3.5	33	-0.23	0.51	-1.5	0.6
		SB 207499	58	1.87	0.70	0.9	4.0	58	-0.23	0.57	-2.1	0.9
	VISIT 37/WEEK 13	PLACEBO	1	2.89	.	2.9	2.9	1	0.33	.	0.3	0.3
		SB 207499	2	2.15	1.18	1.3	3.0	2	0.26	0.64	-0.2	0.7
ENDPOINT		PLACEBO	239	1.93	0.96	0.6	13.1	239	-0.15	0.67	-2.0	6.6
		SB 207499	472	1.95	0.73	0.8	9.4	470	-0.16	0.54	-2.1	4.2

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Monocytes Absolute (10 ⁹ /L)	BASELINE	PLACEBO	243	0.52	0.23	0.2	2.0	0	.	.	.	.
		SB 207499	478	0.53	0.25	0.1	3.2	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	234	0.46	0.19	0.0	1.2	234	-0.05	0.20	-0.9	0.5
		SB 207499	460	0.48	0.20	0.0	1.3	458	-0.05	0.24	-2.6	0.8
	VISIT 2/WEEK 1	PLACEBO	229	0.48	0.22	0.0	1.8	229	-0.04	0.21	-0.9	0.9
		SB 207499	446	0.48	0.22	0.0	2.2	444	-0.05	0.27	-2.5	2.0
	VISIT 3/WEEK 2	PLACEBO	218	0.48	0.20	0.1	1.3	218	-0.04	0.20	-0.9	0.6
		SB 207499	449	0.49	0.20	0.1	1.7	448	-0.04	0.25	-2.7	1.0
	VISIT 4/WEEK 4	PLACEBO	212	0.48	0.21	0.1	2.0	212	-0.04	0.23	-0.9	1.5
		SB 207499	443	0.51	0.21	0.0	1.8	442	-0.03	0.24	-2.7	0.7
	VISIT 5/WEEK 8	PLACEBO	203	0.51	0.26	0.1	2.2	203	-0.01	0.23	-1.0	0.7
		SB 207499	431	0.52	0.25	0.1	2.8	430	-0.01	0.27	-2.6	1.8
	VISIT 6/WEEK 12	PLACEBO	201	0.50	0.23	0.1	2.0	201	-0.02	0.23	-1.0	1.0
		SB 207499	426	0.50	0.20	0.1	1.8	425	-0.03	0.26	-2.6	1.1
	VISIT 7/WEEK 16	PLACEBO	195	0.50	0.20	0.1	1.2	195	-0.02	0.21	-0.9	0.7
		SB 207499	417	0.50	0.19	0.0	1.8	416	-0.02	0.23	-2.7	0.7
	VISIT 8/WEEK 20	PLACEBO	193	0.50	0.20	0.2	1.3	193	-0.02	0.21	-1.0	0.7
		SB 207499	419	0.51	0.19	0.1	1.4	418	-0.02	0.23	-2.7	0.7
	VISIT 9/WEEK 24	PLACEBO	187	0.51	0.20	0.1	1.5	187	-0.01	0.19	-0.7	1.0
		SB 207499	419	0.51	0.23	0.0	2.6	418	-0.02	0.25	-2.6	2.0
	VISIT 10/WEEK 28	PLACEBO	184	0.49	0.17	0.2	1.0	184	-0.03	0.21	-1.2	0.4
		SB 207499	412	0.51	0.19	0.0	1.7	411	-0.02	0.23	-2.8	0.9
	VISIT 11/WEEK 32	PLACEBO	184	0.50	0.18	0.1	1.1	184	-0.02	0.18	-1.1	0.4
		SB 207499	408	0.50	0.20	0.1	1.4	407	-0.01	0.18	-0.8	1.0
	VISIT 12/WEEK 36	PLACEBO	181	0.49	0.18	0.2	1.1	181	-0.03	0.21	-1.3	0.5
		SB 207499	407	0.51	0.21	0.0	1.5	406	-0.01	0.20	-0.7	1.2
	VISIT 13/WEEK 40	PLACEBO	177	0.51	0.18	0.1	1.3	177	-0.01	0.23	-1.1	0.7
		SB 207499	398	0.51	0.20	0.0	1.2	397	-0.00	0.19	-0.7	0.7
	VISIT 14/WEEK 44	PLACEBO	181	0.52	0.20	0.0	1.3	181	-0.01	0.22	-1.0	0.5
		SB 207499	397	0.52	0.20	0.0	1.4	396	-0.00	0.19	-0.6	1.2

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Monocytes Absolute (10 ⁹ /L)	VISIT 15/WEEK 48	PLACEBO	180	0.51	0.20	0.1	1.6	180	-0.01	0.21	-1.0	0.6
		SB 207499	396	0.52	0.20	0.0	1.3	395	0.00	0.19	-0.7	0.7
	VISIT 16/WEEK 52	PLACEBO	176	0.53	0.21	0.1	1.4	176	-0.00	0.23	-1.2	0.8
		SB 207499	375	0.53	0.20	0.1	1.3	374	0.01	0.21	-0.7	0.9
	VISIT 17/WEEK 56	PLACEBO	165	0.52	0.22	0.0	1.4	165	0.00	0.23	-0.9	0.7
		SB 207499	355	0.55	0.21	0.1	1.8	355	0.03	0.21	-0.7	0.9
	VISIT 18/WEEK 60	PLACEBO	165	0.54	0.21	0.2	1.5	165	0.02	0.23	-1.0	0.8
		SB 207499	365	0.56	0.22	0.0	1.3	365	0.04	0.21	-0.5	0.9
	VISIT 19/WEEK 64	PLACEBO	138	0.55	0.22	0.2	1.9	138	0.00	0.21	-1.0	0.5
		SB 207499	295	0.55	0.21	0.0	1.5	295	0.03	0.20	-0.6	1.0
	VISIT 20/WEEK 68	PLACEBO	137	0.57	0.24	0.1	1.6	137	0.02	0.23	-0.9	1.0
		SB 207499	294	0.56	0.24	0.1	1.7	294	0.04	0.21	-0.6	1.0
	VISIT 21/WEEK 72	PLACEBO	167	0.53	0.22	0.2	1.4	167	0.01	0.20	-0.9	0.7
		SB 207499	350	0.55	0.21	0.0	1.4	349	0.04	0.19	-0.6	0.8
	VISIT 22/WEEK 76	PLACEBO	95	0.56	0.26	0.1	1.6	95	0.01	0.21	-0.6	0.9
		SB 207499	195	0.54	0.23	0.0	1.4	195	0.02	0.19	-0.9	0.6
	VISIT 23/WEEK 80	PLACEBO	98	0.55	0.22	0.1	1.5	98	-0.00	0.21	-1.0	0.9
		SB 207499	187	0.55	0.26	0.2	1.9	187	0.04	0.21	-0.6	1.0
	VISIT 24/WEEK 84	PLACEBO	161	0.52	0.20	0.1	1.3	161	-0.00	0.22	-1.0	0.5
		SB 207499	331	0.51	0.19	0.0	1.5	330	0.01	0.18	-0.6	0.5
	VISIT 25/WEEK 88	PLACEBO	51	0.54	0.27	0.2	1.6	51	-0.03	0.20	-0.6	0.4
		SB 207499	95	0.52	0.28	0.2	2.5	95	0.01	0.22	-0.5	1.3
	VISIT 26/WEEK 92	PLACEBO	51	0.54	0.20	0.2	1.0	51	-0.03	0.24	-1.2	0.3
		SB 207499	95	0.52	0.21	0.2	1.2	95	0.01	0.19	-0.5	0.5
	VISIT 27/WEEK 96	PLACEBO	155	0.51	0.19	0.1	1.2	155	-0.01	0.26	-1.5	0.6
		SB 207499	324	0.50	0.25	0.1	3.2	324	0.00	0.26	-0.6	3.0
	VISIT 28/WEEK 10	PLACEBO	20	0.56	0.21	0.3	1.2	20	-0.11	0.37	-1.4	0.3
		SB 207499	48	0.48	0.24	0.1	1.4	48	-0.04	0.22	-0.5	0.8
	VISIT 29/WEEK 10	PLACEBO	18	0.51	0.22	0.2	1.0	18	-0.18	0.30	-1.0	0.2
		SB 207499	39	0.53	0.19	0.2	1.0	39	0.02	0.18	-0.4	0.5

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Monocytes Absolute (10 ⁹ /L)	VISIT 30/WEEK 10	PLACEBO	128	0.52	0.16	0.1	1.0	128	-0.02	0.23	-1.3	0.5
		SB 207499	265	0.52	0.22	0.0	1.6	265	0.01	0.21	-0.7	0.6
	VISIT 31/WEEK 11	PLACEBO	8	0.48	0.12	0.3	0.7	8	-0.14	0.24	-0.7	0.1
		SB 207499	17	0.54	0.21	0.2	1.0	17	0.03	0.18	-0.2	0.5
	VISIT 32/WEEK 11	PLACEBO	9	0.48	0.17	0.1	0.7	9	-0.15	0.29	-0.7	0.2
		SB 207499	16	0.48	0.26	0.1	0.9	16	-0.05	0.23	-0.6	0.4
	VISIT 33/WEEK 12	PLACEBO	87	0.54	0.21	0.2	1.2	87	-0.03	0.21	-1.0	0.4
		SB 207499	184	0.53	0.21	0.1	1.3	184	-0.01	0.21	-1.1	0.5
	VISIT 34/WEEK 12	PLACEBO	3	0.47	0.10	0.4	0.6	3	-0.00	0.22	-0.2	0.2
		SB 207499	3	0.73	0.19	0.5	0.9	3	0.03	0.19	-0.1	0.2
	VISIT 35/WEEK 12	PLACEBO	3	0.71	0.32	0.5	1.1	3	0.24	0.37	-0.1	0.6
		SB 207499	3	0.55	0.41	0.1	0.9	3	-0.15	0.20	-0.4	0.0
	VISIT 36/WEEK 13	PLACEBO	33	0.54	0.20	0.1	1.0	33	-0.04	0.19	-0.6	0.4
		SB 207499	58	0.53	0.22	0.0	1.0	58	-0.04	0.19	-0.5	0.4
	VISIT 37/WEEK 13	PLACEBO	1	0.39	.	0.4	0.4	1	-0.07	.	-0.1	-0.1
		SB 207499	2	0.61	0.04	0.6	0.6	2	0.02	0.08	-0.0	0.1
ENDPOINT		PLACEBO	239	0.53	0.22	0.1	2.0	239	0.02	0.23	-1.0	1.5
		SB 207499	472	0.54	0.21	0.0	1.6	470	0.01	0.26	-2.8	1.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Neutrophils Absolute (10 ⁹ /L)	BASELINE	PLACEBO	243	4.86	1.72	1.7	15.8	0	.	.	.	.
		SB 207499	478	4.68	1.65	1.0	14.5	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	234	4.59	1.79	1.6	18.9	234	-0.25	1.85	-9.7	11.7
		SB 207499	460	4.65	1.77	1.1	14.3	458	-0.03	1.64	-8.5	9.0
	VISIT 2/WEEK 1	PLACEBO	229	4.44	1.44	0.9	11.8	229	-0.45	1.69	-11.5	5.5
		SB 207499	446	4.72	1.95	1.6	17.3	444	0.00	1.78	-8.0	11.3
	VISIT 3/WEEK 2	PLACEBO	218	4.43	1.51	1.2	12.6	218	-0.45	1.69	-10.3	9.2
		SB 207499	449	4.69	1.84	1.8	16.1	448	0.01	1.72	-7.0	7.4
	VISIT 4/WEEK 4	PLACEBO	212	4.54	1.55	1.1	12.7	212	-0.35	1.81	-9.4	9.3
		SB 207499	443	4.67	1.88	1.0	16.4	442	-0.04	1.77	-8.5	10.6
	VISIT 5/WEEK 8	PLACEBO	203	4.69	1.62	1.5	11.6	203	-0.21	1.77	-7.1	5.5
		SB 207499	431	4.75	1.88	2.1	18.3	430	0.03	1.89	-11.1	10.1
	VISIT 6/WEEK 12	PLACEBO	201	4.77	1.81	1.1	13.6	201	-0.13	2.07	-11.7	8.8
		SB 207499	426	4.73	1.88	1.0	23.3	425	0.06	1.67	-6.8	8.8
	VISIT 7/WEEK 16	PLACEBO	195	4.58	1.51	1.6	9.7	195	-0.32	1.70	-10.0	3.9
		SB 207499	417	4.71	1.77	1.9	18.5	416	0.04	1.68	-5.8	14.6
	VISIT 8/WEEK 20	PLACEBO	193	4.63	1.43	1.9	9.0	193	-0.30	1.59	-10.3	3.6
		SB 207499	419	4.82	1.83	1.7	15.0	418	0.07	1.81	-8.3	8.9
	VISIT 9/WEEK 24	PLACEBO	187	4.66	1.49	1.6	11.3	187	-0.30	1.68	-10.5	5.1
		SB 207499	419	4.71	1.71	1.2	12.3	418	0.01	1.56	-7.5	5.9
	VISIT 10/WEEK 28	PLACEBO	184	4.59	1.30	1.4	7.9	184	-0.38	1.66	-10.6	3.3
		SB 207499	412	4.72	1.69	1.3	13.0	411	0.00	1.55	-7.3	8.6
	VISIT 11/WEEK 32	PLACEBO	184	4.68	1.65	1.5	14.6	184	-0.25	1.84	-11.3	7.4
		SB 207499	408	4.75	1.76	1.3	16.0	407	0.06	1.60	-6.8	10.7
	VISIT 12/WEEK 36	PLACEBO	181	4.59	1.69	1.3	13.3	181	-0.32	1.89	-10.6	8.4
		SB 207499	407	4.60	1.44	1.6	9.8	406	-0.12	1.48	-7.5	5.2
	VISIT 13/WEEK 40	PLACEBO	177	4.59	1.39	1.7	9.6	177	-0.34	1.78	-11.4	4.0
		SB 207499	398	4.81	1.86	1.6	19.2	397	0.10	1.73	-6.3	15.8
	VISIT 14/WEEK 44	PLACEBO	181	4.75	1.57	1.1	13.3	181	-0.23	1.86	-10.9	7.8
		SB 207499	397	4.72	1.61	1.3	12.2	396	0.01	1.52	-4.9	7.7

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Neutrophils Absolute (10 ⁹ /L)	VISIT 15/WEEK 48	PLACEBO	180	4.71	1.44	1.3	11.5	180	-0.23	1.92	-10.7	7.6
		SB 207499	396	4.71	1.72	1.7	15.8	395	0.00	1.60	-5.6	12.9
	VISIT 16/WEEK 52	PLACEBO	176	4.95	1.89	1.0	17.6	176	-0.04	2.12	-8.6	10.5
		SB 207499	375	4.74	1.72	0.2	12.4	374	0.02	1.70	-6.9	6.0
	VISIT 17/WEEK 56	PLACEBO	165	4.71	1.62	1.7	15.6	165	-0.26	1.89	-9.5	9.4
		SB 207499	355	4.73	1.70	0.5	10.8	355	0.07	1.70	-5.1	9.0
	VISIT 18/WEEK 60	PLACEBO	165	4.60	1.64	0.9	9.7	165	-0.32	1.91	-9.2	5.7
		SB 207499	365	4.79	1.75	0.9	11.9	365	0.10	1.80	-10.6	8.3
	VISIT 19/WEEK 64	PLACEBO	138	4.70	1.46	1.7	8.6	138	-0.29	1.61	-5.3	3.6
		SB 207499	295	4.77	1.61	0.4	12.8	295	0.08	1.59	-6.7	7.1
	VISIT 20/WEEK 68	PLACEBO	137	4.62	1.64	1.3	13.9	137	-0.33	1.90	-7.2	8.6
		SB 207499	294	4.72	1.84	1.6	14.6	294	0.10	1.76	-5.7	9.3
	VISIT 21/WEEK 72	PLACEBO	167	4.74	1.53	1.5	11.4	167	-0.22	1.89	-10.5	6.2
		SB 207499	350	4.72	1.59	1.5	13.2	349	0.05	1.63	-5.0	8.0
	VISIT 22/WEEK 76	PLACEBO	95	4.73	1.88	1.1	14.3	95	-0.09	2.00	-5.7	9.3
		SB 207499	195	4.72	1.76	0.3	13.0	195	0.13	1.62	-5.5	6.7
	VISIT 23/WEEK 80	PLACEBO	98	4.68	1.54	0.4	8.8	98	-0.18	1.62	-6.9	3.6
		SB 207499	187	4.71	1.94	1.0	17.6	187	0.15	1.63	-3.9	9.4
	VISIT 24/WEEK 84	PLACEBO	161	4.74	1.65	0.7	11.3	161	-0.17	2.04	-10.4	8.0
		SB 207499	331	4.80	1.72	0.3	12.8	330	0.15	1.69	-5.9	6.8
	VISIT 25/WEEK 88	PLACEBO	51	4.60	1.33	2.2	10.3	51	-0.39	1.76	-5.6	4.0
		SB 207499	95	4.48	1.90	1.1	15.4	95	-0.18	1.64	-5.5	5.0
	VISIT 26/WEEK 92	PLACEBO	51	4.91	1.82	2.5	9.7	51	-0.07	1.88	-5.5	3.8
		SB 207499	95	4.64	1.74	1.3	11.0	95	-0.01	1.60	-4.3	5.5
	VISIT 27/WEEK 96	PLACEBO	155	4.82	1.77	1.3	14.2	155	-0.17	1.93	-6.8	7.8
		SB 207499	324	4.68	1.54	1.5	12.8	324	0.04	1.54	-6.6	4.7
	VISIT 28/WEEK 10	PLACEBO	20	4.59	1.58	2.5	9.2	20	-0.80	2.18	-6.9	3.6
		SB 207499	48	4.73	2.13	2.2	13.9	48	0.04	2.12	-5.2	7.8
	VISIT 29/WEEK 10	PLACEBO	18	4.20	0.94	2.4	6.2	18	-0.91	1.79	-4.8	1.2
		SB 207499	39	4.82	1.66	2.2	9.0	39	0.08	1.35	-2.8	3.8

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Neutrophils Absolute (10 ⁹ /L)	VISIT 30/WEEK 10	PLACEBO	128	4.92	1.76	1.3	10.6	128	0.00	2.07	-9.2	7.4
		SB 207499	265	4.74	1.83	0.4	14.2	265	0.10	1.64	-5.3	5.0
	VISIT 31/WEEK 11	PLACEBO	8	4.16	0.96	2.9	5.7	8	-0.96	1.56	-3.8	1.4
		SB 207499	17	4.72	1.42	3.0	8.0	17	-0.17	1.16	-2.8	1.4
	VISIT 32/WEEK 11	PLACEBO	9	4.52	2.29	2.7	9.5	9	-0.94	2.18	-4.6	2.1
		SB 207499	16	5.20	1.86	2.9	10.1	16	0.23	2.20	-3.1	4.4
	VISIT 33/WEEK 12	PLACEBO	87	4.89	1.90	2.0	16.0	87	-0.00	1.91	-3.7	9.8
		SB 207499	184	5.08	2.30	0.9	21.0	184	0.31	2.20	-8.2	16.8
	VISIT 34/WEEK 12	PLACEBO	3	4.56	0.95	3.7	5.6	3	0.08	1.12	-0.7	1.4
		SB 207499	3	5.56	1.91	4.5	7.8	3	0.24	1.14	-0.5	1.6
	VISIT 35/WEEK 12	PLACEBO	3	9.14	8.09	4.0	18.5	3	4.66	8.33	-0.4	14.3
		SB 207499	3	7.00	2.58	4.3	9.4	3	1.69	2.48	-0.5	4.4
	VISIT 36/WEEK 13	PLACEBO	33	4.55	1.21	2.5	6.9	33	-0.41	1.64	-4.8	2.5
		SB 207499	58	5.24	1.69	1.2	10.3	58	0.32	2.01	-4.5	5.4
	VISIT 37/WEEK 13	PLACEBO	1	4.34	.	4.3	4.3	1	0.15	.	0.1	0.1
		SB 207499	2	4.97	0.38	4.7	5.2	2	1.11	0.99	0.4	1.8
	ENDPOINT	PLACEBO	239	4.86	1.78	1.3	17.6	239	-0.02	1.97	-9.2	10.5
		SB 207499	472	5.02	1.99	0.9	21.0	470	0.34	1.99	-8.3	16.8

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Sodium (MMOL/L)	BASELINE	PLACEBO	243	140.50	2.79	127.0	147.0	0	.	.	.	.
		SB 207499	476	140.63	2.82	132.0	154.0	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	235	141.36	3.49	126.0	154.0	235	0.90	3.70	-14.0	20.0
		SB 207499	472	141.39	2.62	134.0	150.0	468	0.75	3.02	-16.0	11.0
	VISIT 2/WEEK 1	PLACEBO	233	141.09	2.98	130.0	147.0	233	0.63	3.08	-10.0	9.0
		SB 207499	451	141.14	2.76	127.0	148.0	447	0.51	3.17	-13.0	10.0
	VISIT 3/WEEK 2	PLACEBO	223	141.13	2.75	130.0	148.0	223	0.61	2.91	-8.0	8.0
		SB 207499	451	141.40	2.78	129.0	153.0	449	0.79	3.36	-18.0	16.0
	VISIT 4/WEEK 4	PLACEBO	211	141.01	2.93	126.0	149.0	211	0.47	3.17	-10.0	11.0
		SB 207499	443	141.17	2.81	132.0	149.0	440	0.57	3.33	-11.0	10.0
	VISIT 5/WEEK 8	PLACEBO	209	140.94	3.39	128.0	151.0	209	0.50	3.23	-7.0	12.0
		SB 207499	436	140.97	2.75	130.0	150.0	433	0.41	3.32	-13.0	12.0
	VISIT 6/WEEK 12	PLACEBO	203	141.06	3.04	127.0	149.0	203	0.61	3.20	-9.0	9.0
		SB 207499	436	140.88	2.96	126.0	152.0	433	0.29	3.54	-14.0	10.0
	VISIT 7/WEEK 16	PLACEBO	194	140.68	3.08	129.0	150.0	194	0.23	2.97	-9.0	8.0
		SB 207499	426	140.81	3.05	127.0	151.0	423	0.17	3.52	-12.0	15.0
	VISIT 8/WEEK 20	PLACEBO	193	140.87	2.88	129.0	148.0	193	0.28	2.89	-8.0	9.0
		SB 207499	431	140.93	2.97	131.0	150.0	428	0.30	3.55	-13.0	11.0
	VISIT 9/WEEK 24	PLACEBO	189	140.75	2.78	129.0	148.0	189	0.17	2.93	-7.0	9.0
		SB 207499	420	140.47	2.93	130.0	152.0	417	-0.16	3.40	-13.0	16.0
	VISIT 10/WEEK 28	PLACEBO	184	140.58	2.85	132.0	150.0	184	-0.08	3.11	-8.0	10.0
		SB 207499	414	140.17	2.99	126.0	147.0	411	-0.49	3.22	-14.0	9.0
	VISIT 11/WEEK 32	PLACEBO	186	140.26	2.67	133.0	149.0	186	-0.36	2.86	-8.0	8.0
		SB 207499	413	140.20	2.98	128.0	152.0	410	-0.45	3.35	-12.0	13.0
	VISIT 12/WEEK 36	PLACEBO	184	140.35	2.41	134.0	146.0	184	-0.24	2.80	-8.0	7.0
		SB 207499	405	140.24	2.76	130.0	153.0	402	-0.46	3.11	-15.0	12.0
	VISIT 13/WEEK 40	PLACEBO	180	140.20	2.66	128.0	148.0	180	-0.47	2.61	-10.0	7.0
		SB 207499	397	140.45	2.77	131.0	151.0	394	-0.28	3.09	-16.0	8.0
	VISIT 14/WEEK 44	PLACEBO	180	140.51	2.38	132.0	147.0	180	-0.16	2.70	-9.0	9.0
		SB 207499	398	140.57	2.87	124.0	150.0	395	-0.14	3.24	-15.0	14.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Sodium (MMOL/L)	VISIT 15/WEEK 48	PLACEBO	181	140.73	2.62	133.0	149.0	181	0.09	2.76	-7.0	9.0
		SB 207499	388	140.76	2.81	126.0	149.0	385	0.05	3.07	-13.0	10.0
	VISIT 16/WEEK 52	PLACEBO	177	140.90	2.82	130.0	151.0	177	0.20	2.88	-7.0	13.0
		SB 207499	375	140.80	2.67	125.0	148.0	372	0.15	2.98	-13.0	8.0
	VISIT 17/WEEK 56	PLACEBO	171	140.87	2.43	130.0	146.0	171	0.17	2.70	-7.0	7.0
		SB 207499	359	141.23	2.65	134.0	150.0	356	0.56	2.98	-13.0	8.0
	VISIT 18/WEEK 60	PLACEBO	170	141.01	3.04	120.0	148.0	170	0.32	3.05	-12.0	7.0
		SB 207499	364	141.30	2.42	130.0	148.0	361	0.60	3.07	-11.0	11.0
	VISIT 19/WEEK 64	PLACEBO	139	141.31	2.39	134.0	148.0	139	0.71	2.77	-6.0	7.0
		SB 207499	300	141.65	2.55	132.0	150.0	297	1.13	3.24	-14.0	11.0
	VISIT 20/WEEK 68	PLACEBO	135	141.07	2.58	133.0	147.0	135	0.48	2.99	-7.0	8.0
		SB 207499	292	141.52	2.61	133.0	150.0	289	0.98	3.22	-14.0	11.0
	VISIT 21/WEEK 72	PLACEBO	170	140.96	2.98	126.0	150.0	170	0.27	3.14	-13.0	10.0
		SB 207499	354	141.43	2.63	132.0	150.0	351	0.73	3.16	-13.0	9.0
	VISIT 22/WEEK 76	PLACEBO	97	141.05	2.26	133.0	147.0	97	0.33	2.92	-5.0	8.0
		SB 207499	197	141.17	2.79	132.0	149.0	195	0.78	3.26	-8.0	10.0
	VISIT 23/WEEK 80	PLACEBO	98	141.30	2.55	131.0	147.0	98	0.52	2.81	-8.0	7.0
		SB 207499	187	140.88	2.66	134.0	148.0	186	0.43	3.43	-7.0	12.0
	VISIT 24/WEEK 84	PLACEBO	159	140.79	2.66	127.0	148.0	159	0.09	2.88	-8.0	10.0
		SB 207499	331	140.75	2.72	130.0	153.0	329	0.00	3.10	-12.0	12.0
	VISIT 25/WEEK 88	PLACEBO	52	140.85	2.32	136.0	146.0	52	0.21	2.52	-6.0	5.0
		SB 207499	97	141.08	2.48	135.0	147.0	96	0.15	2.58	-9.0	7.0
	VISIT 26/WEEK 92	PLACEBO	52	140.48	2.82	131.0	146.0	52	-0.21	2.95	-10.0	5.0
		SB 207499	93	141.10	2.61	131.0	147.0	92	0.25	2.69	-7.0	10.0
	VISIT 27/WEEK 96	PLACEBO	160	141.17	2.58	132.0	148.0	160	0.44	2.81	-7.0	7.0
		SB 207499	325	141.23	2.64	131.0	149.0	323	0.45	3.04	-12.0	10.0
	VISIT 28/WEEK 10	PLACEBO	21	140.14	2.92	133.0	144.0	21	-0.48	3.59	-8.0	5.0
		SB 207499	49	141.78	2.39	137.0	146.0	49	1.18	2.53	-6.0	5.0
	VISIT 29/WEEK 10	PLACEBO	18	141.83	2.48	136.0	149.0	18	1.17	2.73	-3.0	9.0
		SB 207499	40	141.93	2.51	132.0	146.0	40	0.90	2.81	-6.0	7.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Sodium (MMOL/L)	VISIT 30/WEEK 10	PLACEBO	130	141.45	2.48	132.0	145.0	130	0.98	2.72	-7.0	8.0
		SB 207499	271	141.80	2.31	134.0	150.0	269	1.13	2.80	-10.0	9.0
	VISIT 31/WEEK 11	PLACEBO	9	141.11	2.09	136.0	143.0	9	0.00	2.35	-4.0	4.0
		SB 207499	18	141.56	2.59	134.0	146.0	18	0.94	2.62	-4.0	5.0
	VISIT 32/WEEK 11	PLACEBO	9	143.00	2.24	141.0	148.0	9	1.89	2.67	-2.0	6.0
		SB 207499	16	142.00	2.42	138.0	146.0	16	1.50	3.27	-6.0	6.0
	VISIT 33/WEEK 12	PLACEBO	88	141.38	2.47	130.0	147.0	88	0.81	2.63	-6.0	8.0
		SB 207499	183	141.45	2.51	134.0	148.0	182	1.07	3.25	-15.0	11.0
	VISIT 34/WEEK 12	PLACEBO	3	143.33	3.06	140.0	146.0	3	0.67	3.21	-3.0	3.0
		SB 207499	3	140.67	2.52	138.0	143.0	3	0.67	3.06	-2.0	4.0
	VISIT 35/WEEK 12	PLACEBO	3	142.00	2.00	140.0	144.0	3	-0.67	2.52	-3.0	2.0
		SB 207499	3	141.33	1.15	140.0	142.0	3	1.33	2.08	-1.0	3.0
	VISIT 36/WEEK 13	PLACEBO	31	141.23	2.63	136.0	146.0	31	0.58	2.80	-4.0	8.0
		SB 207499	58	141.74	2.80	134.0	148.0	57	1.54	3.56	-10.0	9.0
	VISIT 37/WEEK 13	PLACEBO	1	142.00	.	142.0	142.0	1	-1.00	.	-1.0	-1.0
		SB 207499	2	144.50	0.71	144.0	145.0	2	4.50	0.71	4.0	5.0
	ENDPOINT	PLACEBO	239	141.03	3.03	127.0	150.0	239	0.51	3.23	-9.0	9.0
		SB 207499	472	141.35	2.67	131.0	150.0	468	0.76	3.23	-10.0	11.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Potassium (MMOL/L)	BASELINE	PLACEBO	242	4.53	0.38	3.6	5.8	0	.	.	.	.
		SB 207499	476	4.52	0.39	3.5	6.0	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	233	4.51	0.38	3.1	5.8	232	-0.02	0.41	-1.6	0.9
		SB 207499	473	4.49	0.42	3.4	7.8	469	-0.03	0.46	-1.7	3.6
	VISIT 2/WEEK 1	PLACEBO	229	4.49	0.38	2.5	5.9	228	-0.04	0.45	-2.2	1.5
		SB 207499	449	4.48	0.39	3.3	6.1	445	-0.03	0.44	-1.6	1.7
	VISIT 3/WEEK 2	PLACEBO	223	4.51	0.39	3.5	5.9	222	-0.02	0.40	-1.1	1.5
		SB 207499	444	4.48	0.39	3.1	6.0	442	-0.04	0.43	-1.5	1.4
	VISIT 4/WEEK 4	PLACEBO	210	4.48	0.38	3.2	5.9	209	-0.05	0.41	-1.9	1.6
		SB 207499	440	4.46	0.39	3.3	6.0	437	-0.05	0.43	-1.6	1.6
	VISIT 5/WEEK 8	PLACEBO	209	4.51	0.39	3.2	5.8	208	-0.03	0.43	-1.9	1.2
		SB 207499	433	4.44	0.41	3.2	7.4	431	-0.07	0.44	-1.9	2.0
	VISIT 6/WEEK 12	PLACEBO	202	4.49	0.38	3.2	5.4	201	-0.04	0.41	-1.9	1.1
		SB 207499	433	4.47	0.38	3.2	6.9	430	-0.04	0.41	-1.8	1.5
	VISIT 7/WEEK 16	PLACEBO	193	4.48	0.37	3.7	5.5	192	-0.05	0.41	-1.3	1.1
		SB 207499	426	4.46	0.42	2.9	5.7	423	-0.06	0.41	-1.6	1.3
	VISIT 8/WEEK 20	PLACEBO	192	4.49	0.40	3.6	5.8	192	-0.04	0.40	-1.2	1.1
		SB 207499	428	4.47	0.42	3.2	6.1	425	-0.04	0.43	-1.8	1.7
	VISIT 9/WEEK 24	PLACEBO	189	4.51	0.38	3.3	6.0	189	-0.02	0.40	-1.8	1.2
		SB 207499	417	4.47	0.43	3.4	7.2	414	-0.04	0.46	-1.7	2.9
	VISIT 10/WEEK 28	PLACEBO	185	4.49	0.42	3.5	7.1	185	-0.05	0.48	-1.8	3.0
		SB 207499	411	4.44	0.38	3.5	6.1	408	-0.08	0.45	-2.1	1.1
	VISIT 11/WEEK 32	PLACEBO	186	4.44	0.40	2.7	5.7	186	-0.09	0.45	-2.4	1.3
		SB 207499	409	4.45	0.40	3.4	6.2	406	-0.07	0.45	-1.6	1.3
	VISIT 12/WEEK 36	PLACEBO	184	4.51	0.51	3.4	9.0	184	-0.02	0.57	-1.7	4.9
		SB 207499	404	4.43	0.40	3.5	7.1	401	-0.09	0.46	-1.7	1.9
	VISIT 13/WEEK 40	PLACEBO	179	4.45	0.35	3.2	5.5	179	-0.07	0.40	-1.3	1.3
		SB 207499	394	4.43	0.40	3.3	6.2	391	-0.08	0.44	-2.0	1.4
	VISIT 14/WEEK 44	PLACEBO	179	4.45	0.38	2.8	5.8	179	-0.08	0.44	-2.3	1.3
		SB 207499	396	4.46	0.39	3.2	6.2	393	-0.06	0.44	-1.8	1.6

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Potassium (MMOL/L)	VISIT 15/WEEK 48	PLACEBO	181	4.52	0.38	3.5	5.7	181	-0.01	0.44	-1.3	1.4
		SB 207499	386	4.51	0.41	3.4	5.8	383	-0.00	0.46	-1.8	1.5
	VISIT 16/WEEK 52	PLACEBO	177	4.49	0.35	3.5	5.6	177	-0.04	0.40	-1.4	0.9
		SB 207499	373	4.48	0.42	3.4	6.1	370	-0.04	0.46	-2.0	1.6
	VISIT 17/WEEK 56	PLACEBO	167	4.52	0.36	3.5	5.8	167	-0.01	0.40	-1.2	1.1
		SB 207499	357	4.50	0.42	3.5	6.6	354	-0.02	0.43	-1.7	1.4
	VISIT 18/WEEK 60	PLACEBO	170	4.55	0.41	3.4	5.9	170	0.01	0.45	-1.4	1.9
		SB 207499	364	4.51	0.43	3.1	6.1	361	-0.01	0.44	-1.6	1.4
	VISIT 19/WEEK 64	PLACEBO	139	4.52	0.40	3.0	5.6	139	-0.04	0.48	-2.1	1.4
		SB 207499	299	4.50	0.38	3.4	5.6	296	-0.04	0.44	-1.5	1.3
	VISIT 20/WEEK 68	PLACEBO	135	4.58	0.51	3.4	6.8	135	0.03	0.51	-1.7	2.4
		SB 207499	292	4.53	0.42	3.5	5.8	289	-0.00	0.46	-2.0	1.4
	VISIT 21/WEEK 72	PLACEBO	168	4.52	0.36	3.5	5.5	168	-0.03	0.41	-1.4	1.2
		SB 207499	352	4.54	0.39	3.5	6.1	349	0.03	0.46	-1.7	1.7
	VISIT 22/WEEK 76	PLACEBO	97	4.51	0.36	3.5	5.8	97	-0.07	0.45	-1.6	1.1
		SB 207499	197	4.51	0.38	3.2	5.8	195	-0.03	0.48	-1.6	1.6
	VISIT 23/WEEK 80	PLACEBO	98	4.52	0.37	3.1	5.6	98	-0.06	0.44	-2.0	0.8
		SB 207499	187	4.49	0.39	3.2	5.7	186	-0.06	0.46	-1.6	1.2
	VISIT 24/WEEK 84	PLACEBO	159	4.54	0.38	3.6	5.9	159	-0.01	0.44	-1.4	1.3
		SB 207499	330	4.51	0.38	3.5	5.7	328	-0.02	0.48	-1.4	1.4
	VISIT 25/WEEK 88	PLACEBO	52	4.40	0.32	3.9	5.5	52	-0.19	0.42	-1.1	0.6
		SB 207499	97	4.54	0.37	3.8	6.6	96	-0.04	0.45	-1.4	1.9
	VISIT 26/WEEK 92	PLACEBO	52	4.35	0.37	3.2	5.5	52	-0.24	0.44	-1.9	0.5
		SB 207499	93	4.52	0.37	3.8	5.9	92	-0.07	0.50	-1.8	1.3
	VISIT 27/WEEK 96	PLACEBO	160	4.54	0.35	3.4	5.6	160	0.00	0.40	-1.0	1.2
		SB 207499	324	4.50	0.40	3.3	6.6	322	-0.02	0.46	-1.5	2.1
	VISIT 28/WEEK 10	PLACEBO	21	4.54	0.36	4.0	5.5	21	-0.05	0.48	-1.1	1.0
		SB 207499	49	4.54	0.39	4.0	5.5	49	-0.10	0.51	-1.5	1.0
	VISIT 29/WEEK 10	PLACEBO	18	4.51	0.29	4.1	5.0	18	-0.08	0.47	-0.9	0.8
		SB 207499	40	4.55	0.34	3.7	5.2	40	-0.06	0.41	-0.8	1.1

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Potassium (MMOL/L)	VISIT 30/WEEK 10	PLACEBO	130	4.50	0.37	3.5	5.4	130	-0.01	0.46	-1.4	1.3
		SB 207499	271	4.52	0.44	3.6	7.3	269	-0.01	0.49	-1.7	3.0
	VISIT 31/WEEK 11	PLACEBO	9	4.46	0.28	4.1	5.0	9	-0.10	0.28	-0.6	0.3
		SB 207499	18	4.68	0.35	4.2	5.3	18	0.11	0.39	-0.7	0.8
	VISIT 32/WEEK 11	PLACEBO	9	4.50	0.23	4.2	4.9	9	-0.06	0.55	-0.9	0.7
		SB 207499	16	4.71	0.46	4.1	5.9	16	0.11	0.45	-0.5	1.2
	VISIT 33/WEEK 12	PLACEBO	88	4.51	0.40	3.4	5.4	88	-0.06	0.48	-1.5	1.2
		SB 207499	183	4.53	0.47	3.4	8.5	182	-0.05	0.53	-1.9	3.5
	VISIT 34/WEEK 12	PLACEBO	3	4.60	0.52	4.3	5.2	3	0.30	0.44	0.0	0.8
		SB 207499	3	4.50	0.20	4.3	4.7	3	0.10	0.26	-0.1	0.4
	VISIT 35/WEEK 12	PLACEBO	3	4.33	0.55	3.7	4.7	3	0.03	0.55	-0.6	0.4
		SB 207499	3	4.60	0.17	4.4	4.7	3	0.20	0.35	0.0	0.6
	VISIT 36/WEEK 13	PLACEBO	30	4.57	0.38	3.9	5.3	30	-0.05	0.31	-0.8	0.6
		SB 207499	58	4.49	0.40	3.5	5.7	57	-0.03	0.36	-0.8	1.1
	VISIT 37/WEEK 13	PLACEBO	1	4.30	.	4.3	4.3	1	0.00	.	0.0	0.0
		SB 207499	2	4.30	0.14	4.2	4.4	2	0.05	0.35	-0.2	0.3
	ENDPOINT	PLACEBO	239	4.51	0.42	2.5	6.6	238	-0.01	0.47	-2.2	2.1
		SB 207499	472	4.48	0.44	3.2	8.5	468	-0.04	0.47	-2.0	3.5

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Chloride (MMOL/L)	BASELINE	PLACEBO	243	103.82	3.54	90.0	113.0	0	.	.	.	.
		SB 207499	476	103.74	3.28	91.0	112.0	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	235	103.24	4.05	81.0	114.0	235	-0.56	3.90	-16.0	8.0
		SB 207499	473	103.45	3.35	90.0	112.0	469	-0.32	3.63	-14.0	16.0
	VISIT 2/WEEK 1	PLACEBO	233	103.38	3.66	89.0	111.0	233	-0.51	3.68	-12.0	12.0
		SB 207499	450	103.45	3.20	91.0	112.0	446	-0.27	3.37	-11.0	18.0
	VISIT 3/WEEK 2	PLACEBO	223	103.60	3.51	91.0	112.0	223	-0.30	3.78	-11.0	13.0
		SB 207499	451	103.58	3.39	88.0	112.0	449	-0.12	3.57	-12.0	19.0
	VISIT 4/WEEK 4	PLACEBO	212	103.23	3.58	90.0	110.0	212	-0.60	3.97	-11.0	12.0
		SB 207499	443	103.25	3.29	90.0	112.0	440	-0.46	3.48	-11.0	12.0
	VISIT 5/WEEK 8	PLACEBO	209	103.37	3.78	88.0	114.0	209	-0.43	3.74	-11.0	13.0
		SB 207499	436	103.22	3.35	85.0	113.0	433	-0.50	3.42	-15.0	17.0
	VISIT 6/WEEK 12	PLACEBO	203	102.90	3.20	90.0	110.0	203	-0.87	3.47	-12.0	10.0
		SB 207499	436	102.94	3.28	88.0	111.0	433	-0.76	3.32	-11.0	13.0
	VISIT 7/WEEK 16	PLACEBO	194	102.99	3.10	93.0	109.0	194	-0.77	3.29	-11.0	8.0
		SB 207499	427	103.04	3.40	87.0	111.0	424	-0.61	3.50	-14.0	11.0
	VISIT 8/WEEK 20	PLACEBO	193	103.28	3.13	93.0	110.0	193	-0.59	3.27	-11.0	8.0
		SB 207499	431	102.88	3.65	81.0	111.0	428	-0.78	3.51	-23.0	12.0
	VISIT 9/WEEK 24	PLACEBO	189	103.12	3.19	95.0	112.0	189	-0.66	3.21	-9.0	10.0
		SB 207499	420	103.03	3.32	86.0	111.0	417	-0.60	3.35	-11.0	14.0
	VISIT 10/WEEK 28	PLACEBO	185	102.77	3.26	90.0	112.0	185	-1.26	3.38	-16.0	12.0
		SB 207499	414	103.11	3.41	85.0	112.0	411	-0.53	3.39	-10.0	13.0
	VISIT 11/WEEK 32	PLACEBO	186	102.84	3.32	85.0	109.0	186	-1.15	3.49	-21.0	9.0
		SB 207499	413	103.00	3.34	88.0	111.0	410	-0.71	3.46	-13.0	10.0
	VISIT 12/WEEK 36	PLACEBO	184	103.18	3.23	90.0	111.0	184	-0.74	3.78	-16.0	10.0
		SB 207499	405	103.05	3.25	89.0	111.0	402	-0.62	3.40	-11.0	15.0
	VISIT 13/WEEK 40	PLACEBO	180	103.09	3.03	95.0	111.0	180	-0.93	3.18	-12.0	8.0
		SB 207499	397	103.29	3.47	88.0	112.0	394	-0.46	3.35	-15.0	12.0
	VISIT 14/WEEK 44	PLACEBO	180	103.21	3.49	87.0	109.0	180	-0.80	3.72	-19.0	8.0
		SB 207499	398	103.54	3.29	87.0	112.0	395	-0.22	3.34	-10.0	11.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Chloride (MMOL/L)	VISIT 15/WEEK 48	PLACEBO	181	103.39	3.05	91.0	110.0	181	-0.57	3.27	-11.0	11.0
		SB 207499	388	103.43	3.40	87.0	112.0	385	-0.30	3.39	-11.0	12.0
	VISIT 16/WEEK 52	PLACEBO	177	103.52	2.94	93.0	110.0	177	-0.57	3.00	-9.0	9.0
		SB 207499	375	103.41	3.37	87.0	114.0	372	-0.31	3.32	-14.0	11.0
	VISIT 17/WEEK 56	PLACEBO	171	103.53	2.98	93.0	113.0	171	-0.51	3.25	-11.0	9.0
		SB 207499	359	103.63	3.36	88.0	112.0	356	-0.03	3.42	-12.0	17.0
	VISIT 18/WEEK 60	PLACEBO	170	103.36	3.36	87.0	110.0	170	-0.59	3.45	-11.0	8.0
		SB 207499	364	103.47	3.16	90.0	110.0	361	-0.23	3.31	-13.0	12.0
	VISIT 19/WEEK 64	PLACEBO	139	103.78	2.80	94.0	110.0	139	-0.38	3.05	-12.0	8.0
		SB 207499	300	103.94	3.10	93.0	111.0	297	0.44	3.23	-9.0	17.0
	VISIT 20/WEEK 68	PLACEBO	135	103.61	3.20	91.0	109.0	135	-0.50	3.24	-12.0	8.0
		SB 207499	292	103.75	3.17	93.0	112.0	289	0.19	3.34	-12.0	19.0
	VISIT 21/WEEK 72	PLACEBO	170	103.93	3.59	89.0	111.0	170	-0.07	3.49	-10.0	9.0
		SB 207499	354	104.19	3.20	89.0	113.0	351	0.46	3.49	-14.0	15.0
	VISIT 22/WEEK 76	PLACEBO	97	103.85	2.73	90.0	109.0	97	-0.70	3.30	-16.0	6.0
		SB 207499	197	103.80	3.24	93.0	113.0	195	0.47	3.50	-10.0	13.0
	VISIT 23/WEEK 80	PLACEBO	98	103.81	3.54	88.0	109.0	98	-0.76	4.05	-21.0	8.0
		SB 207499	187	104.03	2.95	93.0	111.0	186	0.66	3.26	-8.0	15.0
	VISIT 24/WEEK 84	PLACEBO	159	103.86	3.08	91.0	112.0	159	-0.10	3.44	-11.0	10.0
		SB 207499	331	103.98	3.18	92.0	112.0	329	0.16	3.23	-10.0	15.0
	VISIT 25/WEEK 88	PLACEBO	52	104.02	2.44	97.0	110.0	52	-0.33	3.24	-10.0	6.0
		SB 207499	97	104.28	2.81	98.0	111.0	96	0.39	3.42	-7.0	17.0
	VISIT 26/WEEK 92	PLACEBO	52	104.27	3.13	90.0	110.0	52	-0.25	3.70	-16.0	6.0
		SB 207499	93	104.47	2.95	96.0	112.0	92	0.63	3.16	-6.0	13.0
	VISIT 27/WEEK 96	PLACEBO	160	103.85	2.97	92.0	111.0	160	-0.10	3.27	-8.0	9.0
		SB 207499	325	104.26	3.17	94.0	113.0	323	0.42	3.31	-12.0	16.0
	VISIT 28/WEEK 10	PLACEBO	21	102.90	3.42	92.0	108.0	21	-0.67	3.04	-8.0	4.0
		SB 207499	49	104.35	2.31	99.0	109.0	49	0.90	2.50	-5.0	6.0
	VISIT 29/WEEK 10	PLACEBO	18	104.50	4.33	99.0	119.0	18	0.89	5.55	-6.0	20.0
		SB 207499	40	103.85	2.75	96.0	109.0	40	0.65	2.59	-4.0	6.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Chloride (MMOL/L)	VISIT 30/WEEK 10	PLACEBO	130	104.20	3.59	91.0	114.0	130	0.62	3.30	-6.0	12.0
		SB 207499	271	104.64	3.31	94.0	114.0	269	0.90	3.19	-8.0	13.0
	VISIT 31/WEEK 11	PLACEBO	9	104.67	2.96	101.0	110.0	9	1.56	3.21	-2.0	7.0
		SB 207499	18	104.17	2.94	97.0	110.0	18	1.78	2.41	-3.0	5.0
	VISIT 32/WEEK 11	PLACEBO	9	104.56	2.55	101.0	109.0	9	1.44	3.28	-4.0	6.0
		SB 207499	16	103.31	2.91	96.0	107.0	16	1.38	1.41	-1.0	4.0
	VISIT 33/WEEK 12	PLACEBO	88	104.15	2.97	95.0	110.0	88	0.20	3.35	-7.0	10.0
		SB 207499	183	104.31	3.34	93.0	111.0	182	0.95	3.04	-6.0	13.0
	VISIT 34/WEEK 12	PLACEBO	3	105.33	2.08	103.0	107.0	3	1.67	2.52	-1.0	4.0
		SB 207499	3	102.33	3.06	99.0	105.0	3	1.00	1.73	0.0	3.0
	VISIT 35/WEEK 12	PLACEBO	3	103.67	2.52	101.0	106.0	3	0.00	3.00	-3.0	3.0
		SB 207499	3	102.33	2.52	100.0	105.0	3	1.00	2.00	-1.0	3.0
	VISIT 36/WEEK 13	PLACEBO	31	104.42	2.66	97.0	110.0	31	-0.23	2.88	-5.0	6.0
		SB 207499	58	103.48	3.67	92.0	110.0	57	0.88	3.88	-14.0	18.0
	VISIT 37/WEEK 13	PLACEBO	1	110.00	.	110.0	110.0	1	6.00	.	6.0	6.0
		SB 207499	2	104.50	3.54	102.0	107.0	2	4.00	1.41	3.0	5.0
	ENDPOINT	PLACEBO	239	103.67	3.48	89.0	111.0	239	-0.18	3.58	-9.0	10.0
		SB 207499	472	104.11	3.43	92.0	114.0	468	0.41	3.37	-14.0	18.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Blood Urea Nitrogen (MMOL/L)	BASELINE	PLACEBO	243	5.64	1.81	1.6	12.5	0	.	.	.	.
		SB 207499	476	5.64	1.72	1.9	18.1	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	233	5.90	2.00	1.7	17.2	233	0.25	1.46	-5.5	10.1
		SB 207499	468	5.58	1.78	1.5	18.1	464	-0.03	1.32	-5.3	4.7
	VISIT 2/WEEK 1	PLACEBO	232	5.81	1.96	1.7	13.4	232	0.18	1.34	-4.2	6.3
		SB 207499	447	5.62	1.85	1.5	20.7	443	-0.04	1.35	-5.1	7.3
	VISIT 3/WEEK 2	PLACEBO	221	5.78	1.87	1.5	13.9	221	0.16	1.34	-5.5	4.4
		SB 207499	449	5.63	1.88	1.6	18.3	447	-0.03	1.33	-5.4	4.7
	VISIT 4/WEEK 4	PLACEBO	212	5.74	1.86	1.3	11.1	212	0.08	1.35	-5.1	6.2
		SB 207499	443	5.61	2.00	1.2	24.2	440	-0.04	1.52	-5.7	13.0
	VISIT 5/WEEK 8	PLACEBO	207	5.75	1.82	1.4	11.8	207	0.06	1.37	-4.8	5.3
		SB 207499	436	5.53	1.81	1.3	13.9	433	-0.12	1.34	-5.1	4.6
	VISIT 6/WEEK 12	PLACEBO	203	5.68	1.81	1.7	11.9	203	0.08	1.35	-5.9	3.6
		SB 207499	435	5.62	1.74	1.7	13.2	432	-0.01	1.37	-4.9	6.8
	VISIT 7/WEEK 16	PLACEBO	193	5.69	1.85	1.7	12.6	193	0.08	1.35	-4.5	4.4
		SB 207499	425	5.66	1.76	1.4	14.4	422	0.05	1.28	-4.4	3.8
	VISIT 8/WEEK 20	PLACEBO	193	5.61	1.71	2.0	13.1	193	0.01	1.33	-4.9	3.6
		SB 207499	429	5.67	1.78	1.5	12.1	426	0.06	1.34	-4.6	4.2
	VISIT 9/WEEK 24	PLACEBO	188	5.70	1.75	1.4	13.8	188	0.04	1.38	-5.1	4.9
		SB 207499	420	5.63	1.75	1.5	13.0	417	0.03	1.34	-4.6	4.2
	VISIT 10/WEEK 28	PLACEBO	183	5.70	1.83	1.2	14.6	183	0.13	1.31	-5.7	3.6
		SB 207499	414	5.63	1.83	1.4	13.6	411	0.01	1.32	-6.0	5.3
	VISIT 11/WEEK 32	PLACEBO	186	5.73	1.87	1.8	14.2	186	0.11	1.46	-5.9	5.3
		SB 207499	412	5.71	1.75	1.6	13.8	409	0.07	1.27	-5.2	4.9
	VISIT 12/WEEK 36	PLACEBO	184	5.73	1.88	1.6	12.8	184	0.14	1.39	-5.1	4.4
		SB 207499	405	5.70	1.73	1.9	14.3	402	0.05	1.27	-4.9	5.3
	VISIT 13/WEEK 40	PLACEBO	179	5.80	1.95	1.8	13.5	179	0.18	1.43	-5.8	4.4
		SB 207499	393	5.79	1.92	2.2	22.0	390	0.15	1.51	-3.9	15.0
	VISIT 14/WEEK 44	PLACEBO	180	5.73	1.87	2.0	13.0	180	0.13	1.58	-5.8	4.1
		SB 207499	397	5.70	1.82	2.0	14.3	394	0.05	1.40	-5.6	5.3

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Blood Urea Nitrogen (MMOL/L)	VISIT 15/WEEK 48	PLACEBO	180	5.75	1.87	1.5	14.8	180	0.14	1.46	-5.7	3.6
		SB 207499	385	5.70	1.80	2.3	13.6	382	0.05	1.44	-5.3	6.6
	VISIT 16/WEEK 52	PLACEBO	177	5.73	1.85	1.1	12.0	177	0.13	1.44	-6.8	3.4
		SB 207499	372	5.73	1.82	1.7	16.0	369	0.07	1.45	-5.4	4.8
	VISIT 17/WEEK 56	PLACEBO	168	5.68	1.80	2.2	12.7	168	0.02	1.46	-6.8	5.0
		SB 207499	357	5.70	1.67	1.1	12.9	354	0.01	1.31	-4.9	3.9
	VISIT 18/WEEK 60	PLACEBO	169	5.76	1.95	1.6	13.4	169	0.11	1.55	-5.3	4.2
		SB 207499	361	5.78	1.67	2.0	11.5	358	0.09	1.39	-5.0	5.0
	VISIT 19/WEEK 64	PLACEBO	137	5.67	1.95	2.1	14.7	137	0.11	1.45	-4.5	3.9
		SB 207499	296	5.80	1.73	1.3	11.9	293	0.13	1.22	-4.2	3.4
	VISIT 20/WEEK 68	PLACEBO	135	5.80	1.92	2.0	13.5	135	0.21	1.50	-3.6	5.8
		SB 207499	291	5.74	1.85	1.8	14.3	288	0.07	1.38	-6.4	5.0
	VISIT 21/WEEK 72	PLACEBO	169	5.73	1.84	2.5	13.5	169	0.12	1.61	-5.9	5.5
		SB 207499	352	5.63	1.63	2.2	11.4	349	0.01	1.36	-5.1	4.9
	VISIT 22/WEEK 76	PLACEBO	97	5.96	1.96	1.4	13.6	97	0.35	1.45	-3.0	5.5
		SB 207499	196	5.68	1.73	2.1	12.8	194	0.01	1.26	-2.8	5.5
	VISIT 23/WEEK 80	PLACEBO	98	5.81	2.02	2.0	14.3	98	0.18	1.22	-2.7	4.1
		SB 207499	187	5.81	1.78	2.2	14.7	186	0.14	1.33	-3.0	5.7
	VISIT 24/WEEK 84	PLACEBO	159	5.83	1.78	2.2	13.0	159	0.14	1.54	-5.8	5.3
		SB 207499	329	5.73	1.87	1.3	11.8	327	0.08	1.50	-4.7	6.4
	VISIT 25/WEEK 88	PLACEBO	52	5.78	2.01	2.3	11.2	52	0.12	1.51	-2.9	4.3
		SB 207499	97	5.99	1.79	2.2	14.5	96	0.08	1.25	-3.3	3.8
	VISIT 26/WEEK 92	PLACEBO	52	5.85	1.80	2.7	10.4	52	0.16	1.34	-2.9	3.6
		SB 207499	93	6.04	1.72	2.5	11.4	92	0.11	1.28	-2.5	3.2
	VISIT 27/WEEK 96	PLACEBO	158	5.93	1.87	2.2	11.5	158	0.26	1.62	-5.0	4.7
		SB 207499	322	5.72	1.78	1.5	13.1	320	0.12	1.44	-4.9	4.8
	VISIT 28/WEEK 10	PLACEBO	21	6.75	2.74	3.6	14.9	21	1.08	2.35	-2.0	9.6
		SB 207499	49	5.98	1.82	3.2	11.1	49	0.04	1.46	-4.0	3.4
	VISIT 29/WEEK 10	PLACEBO	18	6.30	1.79	3.7	11.3	18	0.23	1.90	-2.4	3.5
		SB 207499	40	5.80	1.42	2.6	9.8	40	-0.28	1.08	-2.2	1.8

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Blood Urea Nitrogen (MMOL/L)	VISIT 30/WEEK 10	PLACEBO	129	5.81	1.92	1.9	11.8	129	0.07	1.68	-6.3	5.1
		SB 207499	269	5.66	1.77	2.0	12.9	267	0.04	1.40	-5.2	4.7
	VISIT 31/WEEK 11	PLACEBO	9	6.71	1.21	5.1	8.5	9	0.46	1.68	-1.3	3.0
		SB 207499	18	5.25	1.39	2.5	7.5	18	-0.28	1.41	-2.5	2.2
	VISIT 32/WEEK 11	PLACEBO	9	7.08	1.37	4.2	8.3	9	0.82	1.64	-1.8	3.6
		SB 207499	16	5.36	1.16	3.8	7.3	16	-0.32	1.12	-2.6	1.1
	VISIT 33/WEEK 12	PLACEBO	88	5.78	1.79	0.9	10.2	88	0.06	1.64	-3.7	5.0
		SB 207499	182	5.65	1.68	2.3	10.4	181	0.13	1.32	-4.8	4.2
	VISIT 34/WEEK 12	PLACEBO	3	5.93	1.11	4.9	7.1	3	-0.97	1.48	-2.6	0.3
		SB 207499	3	5.50	1.08	4.6	6.7	3	0.27	2.05	-2.0	2.0
	VISIT 35/WEEK 12	PLACEBO	3	6.23	0.91	5.4	7.2	3	-0.67	0.95	-1.4	0.4
		SB 207499	3	4.90	0.70	4.2	5.6	3	-0.33	1.36	-1.6	1.1
	VISIT 36/WEEK 13	PLACEBO	31	5.55	1.71	2.9	9.4	31	0.10	1.33	-2.4	3.0
		SB 207499	58	5.81	1.78	2.2	11.7	57	0.14	1.52	-3.4	6.1
	VISIT 37/WEEK 13	PLACEBO	1	6.20	.	6.2	6.2	1	-0.20	.	-0.2	-0.2
		SB 207499	2	4.45	0.21	4.3	4.6	2	0.20	0.85	-0.4	0.8
	ENDPOINT	PLACEBO	238	5.68	1.78	0.9	11.8	238	0.05	1.46	-6.3	5.1
		SB 207499	472	5.63	1.81	1.6	13.9	468	-0.01	1.47	-5.7	6.1

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Creatinine (UMOL/L)	BASELINE	PLACEBO	243	76.08	19.52	35.0	167.0	0	.	.	.	.
		SB 207499	476	75.61	19.79	26.0	291.0	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	231	77.74	20.70	36.0	156.0	231	1.29	11.92	-30.0	39.0
		SB 207499	471	75.41	21.33	38.0	331.0	467	-0.22	12.85	-67.0	56.0
	VISIT 2/WEEK 1	PLACEBO	230	76.50	19.44	9.0	147.0	230	0.30	12.67	-52.0	64.0
		SB 207499	449	75.55	27.43	27.0	440.0	445	-0.36	21.48	-30.0	384.0
	VISIT 3/WEEK 2	PLACEBO	221	77.61	19.58	32.0	158.0	221	1.42	12.87	-30.0	59.0
		SB 207499	447	74.71	20.65	36.0	340.0	445	-0.96	11.76	-45.0	66.0
	VISIT 4/WEEK 4	PLACEBO	212	77.87	19.75	36.0	172.0	212	1.32	12.65	-32.0	47.0
		SB 207499	440	74.16	20.24	37.0	330.0	437	-1.40	11.53	-36.0	42.0
	VISIT 5/WEEK 8	PLACEBO	208	77.40	19.05	33.0	159.0	208	1.05	11.45	-40.0	56.0
		SB 207499	433	74.61	20.11	34.0	294.0	431	-1.38	11.76	-42.0	49.0
	VISIT 6/WEEK 12	PLACEBO	202	76.57	18.41	29.0	146.0	202	0.53	13.10	-47.0	43.0
		SB 207499	432	74.02	16.88	22.0	139.0	429	-1.23	12.10	-43.0	47.0
	VISIT 7/WEEK 16	PLACEBO	193	76.77	19.65	40.0	148.0	193	0.73	12.03	-34.0	55.0
		SB 207499	424	73.63	17.83	35.0	166.0	421	-1.65	12.17	-42.0	62.0
	VISIT 8/WEEK 20	PLACEBO	192	74.90	17.66	35.0	161.0	192	-0.74	10.89	-48.0	27.0
		SB 207499	429	74.40	17.93	28.0	167.0	426	-1.07	12.52	-66.0	60.0
	VISIT 9/WEEK 24	PLACEBO	189	75.91	19.42	38.0	160.0	189	-0.63	10.92	-37.0	32.0
		SB 207499	418	74.73	17.91	37.0	167.0	415	-0.99	13.34	-47.0	114.0
	VISIT 10/WEEK 28	PLACEBO	184	76.76	20.00	33.0	161.0	184	0.42	11.39	-37.0	33.0
		SB 207499	411	73.55	17.30	27.0	175.0	408	-2.08	11.49	-46.0	44.0
	VISIT 11/WEEK 32	PLACEBO	186	76.80	19.79	38.0	158.0	186	0.40	10.96	-32.0	34.0
		SB 207499	410	73.64	17.78	33.0	172.0	407	-1.91	11.79	-61.0	55.0
	VISIT 12/WEEK 36	PLACEBO	184	76.99	19.25	40.0	157.0	184	0.63	10.93	-26.0	41.0
		SB 207499	404	75.11	17.09	39.0	152.0	401	-0.39	11.78	-40.0	53.0
	VISIT 13/WEEK 40	PLACEBO	178	76.38	19.63	30.0	154.0	178	0.02	11.62	-28.0	34.0
		SB 207499	392	74.16	18.64	31.0	172.0	389	-1.55	12.01	-37.0	80.0
	VISIT 14/WEEK 44	PLACEBO	179	76.85	20.36	34.0	157.0	179	0.59	13.44	-59.0	63.0
		SB 207499	395	73.64	17.58	29.0	174.0	392	-1.81	11.80	-42.0	57.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Creatinine (UMOL/L)	VISIT 15/WEEK 48	PLACEBO	180	77.08	18.91	38.0	159.0	180	0.76	10.54	-27.0	57.0
		SB 207499	384	74.60	18.57	39.0	181.0	381	-0.86	12.73	-51.0	77.0
	VISIT 16/WEEK 52	PLACEBO	177	76.13	19.83	33.0	156.0	177	-0.32	11.21	-34.0	37.0
		SB 207499	372	73.91	18.70	24.0	178.0	369	-1.61	12.07	-37.0	66.0
	VISIT 17/WEEK 56	PLACEBO	165	75.25	20.42	16.0	161.0	165	-1.18	11.18	-32.0	32.0
		SB 207499	356	73.72	18.19	39.0	167.0	353	-1.70	13.61	-44.0	87.0
	VISIT 18/WEEK 60	PLACEBO	169	75.77	18.68	35.0	156.0	169	-0.49	11.47	-40.0	41.0
		SB 207499	362	75.09	17.09	38.0	162.0	359	-0.31	12.27	-52.0	54.0
	VISIT 19/WEEK 64	PLACEBO	138	75.55	18.73	33.0	147.0	138	-0.07	11.61	-48.0	47.0
		SB 207499	295	74.34	17.65	34.0	168.0	292	-0.60	11.43	-35.0	62.0
	VISIT 20/WEEK 68	PLACEBO	135	77.03	19.70	40.0	146.0	135	1.47	12.29	-38.0	50.0
		SB 207499	292	74.74	18.51	42.0	174.0	289	-0.11	12.57	-40.0	65.0
	VISIT 21/WEEK 72	PLACEBO	170	75.37	19.30	36.0	150.0	170	-0.32	12.04	-33.0	65.0
		SB 207499	352	74.47	17.59	41.0	153.0	349	-0.79	11.65	-43.0	60.0
	VISIT 22/WEEK 76	PLACEBO	97	75.05	22.73	32.0	153.0	97	-0.66	12.96	-36.0	52.0
		SB 207499	196	74.20	18.19	39.0	161.0	194	0.69	12.54	-35.0	61.0
	VISIT 23/WEEK 80	PLACEBO	98	77.11	23.37	36.0	162.0	98	0.70	12.61	-25.0	50.0
		SB 207499	187	74.63	22.10	43.0	247.0	186	1.60	17.55	-38.0	167.0
	VISIT 24/WEEK 84	PLACEBO	159	76.93	19.78	33.0	148.0	159	1.12	12.23	-32.0	54.0
		SB 207499	331	75.77	18.96	39.0	161.0	329	0.46	12.54	-42.0	50.0
	VISIT 25/WEEK 88	PLACEBO	52	77.35	20.75	44.0	146.0	52	0.92	11.09	-20.0	35.0
		SB 207499	97	74.80	17.88	47.0	140.0	96	1.84	12.47	-25.0	35.0
	VISIT 26/WEEK 92	PLACEBO	52	78.23	22.30	40.0	174.0	52	1.85	14.05	-51.0	42.0
		SB 207499	93	77.12	23.13	47.0	231.0	92	4.04	20.96	-23.0	171.0
	VISIT 27/WEEK 96	PLACEBO	159	77.86	21.84	31.0	160.0	159	2.01	15.60	-35.0	96.0
		SB 207499	322	75.52	18.45	40.0	152.0	320	0.65	12.59	-37.0	46.0
	VISIT 28/WEEK 10	PLACEBO	21	80.52	22.59	50.0	149.0	21	2.81	18.51	-28.0	68.0
		SB 207499	49	78.45	18.25	42.0	124.0	49	3.02	13.98	-30.0	40.0
	VISIT 29/WEEK 10	PLACEBO	18	82.44	15.83	57.0	109.0	18	3.22	8.82	-16.0	21.0
		SB 207499	40	78.80	14.26	55.0	112.0	40	3.80	10.91	-18.0	28.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Creatinine (UMOL/L)	VISIT 30/WEEK 10	PLACEBO	130	77.33	21.98	38.0	161.0	130	0.32	14.50	-40.0	72.0
		SB 207499	270	75.53	18.09	27.0	154.0	268	0.75	13.05	-43.0	62.0
	VISIT 31/WEEK 11	PLACEBO	9	82.11	17.30	54.0	103.0	9	0.44	10.08	-16.0	20.0
		SB 207499	18	77.61	17.47	43.0	108.0	18	8.50	12.92	-12.0	32.0
	VISIT 32/WEEK 11	PLACEBO	9	86.67	18.81	61.0	115.0	9	5.00	13.26	-19.0	25.0
		SB 207499	16	76.31	19.08	49.0	107.0	16	7.44	15.61	-12.0	50.0
	VISIT 33/WEEK 12	PLACEBO	87	76.01	19.34	35.0	150.0	87	-0.76	13.59	-38.0	53.0
		SB 207499	182	73.98	17.20	31.0	145.0	181	0.19	11.77	-34.0	43.0
	VISIT 34/WEEK 12	PLACEBO	3	75.67	21.55	55.0	98.0	3	8.67	8.08	4.0	18.0
		SB 207499	3	66.00	8.19	57.0	73.0	3	2.33	12.50	-12.0	11.0
	VISIT 35/WEEK 12	PLACEBO	3	79.00	24.56	52.0	100.0	3	12.00	9.85	1.0	20.0
		SB 207499	3	66.67	1.53	65.0	68.0	3	3.00	4.58	-1.0	8.0
	VISIT 36/WEEK 13	PLACEBO	30	73.70	21.03	40.0	156.0	30	0.07	11.48	-21.0	31.0
		SB 207499	58	74.24	14.93	49.0	116.0	57	2.12	11.45	-29.0	27.0
	VISIT 37/WEEK 13	PLACEBO	1	75.00	.	75.0	75.0	1	5.00	.	5.0	5.0
		SB 207499	2	76.50	14.85	66.0	87.0	2	15.50	9.19	9.0	22.0
	ENDPOINT	PLACEBO	238	75.82	20.52	31.0	161.0	238	-0.20	14.03	-38.0	72.0
		SB 207499	472	74.81	21.32	31.0	294.0	468	-0.91	12.92	-35.0	66.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Uric Acid (UMOL/L)	BASELINE	PLACEBO	243	324.79	91.46	130.0	612.0	0	.	.	.	.
		SB 207499	476	324.71	82.56	120.0	645.0	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	234	331.96	87.95	142.0	603.0	234	7.75	60.17	-267.0	252.0
		SB 207499	473	326.72	80.71	98.0	642.0	469	2.43	55.65	-198.0	282.0
	VISIT 2/WEEK 1	PLACEBO	232	322.68	85.99	126.0	612.0	232	-0.86	64.58	-288.0	221.0
		SB 207499	450	322.42	75.97	107.0	538.0	446	-2.82	55.56	-211.0	210.0
	VISIT 3/WEEK 2	PLACEBO	221	335.27	86.48	117.0	668.0	221	7.66	67.91	-284.0	333.0
		SB 207499	451	322.88	78.98	84.0	602.0	449	-2.63	57.51	-244.0	213.0
	VISIT 4/WEEK 4	PLACEBO	212	331.83	85.00	142.0	656.0	212	6.41	62.69	-310.0	200.0
		SB 207499	443	322.56	78.10	156.0	588.0	440	-1.93	57.86	-242.0	361.0
	VISIT 5/WEEK 8	PLACEBO	208	324.03	81.98	135.0	568.0	208	-1.49	65.37	-294.0	192.0
		SB 207499	436	322.65	78.16	141.0	592.0	433	-3.66	54.83	-203.0	211.0
	VISIT 6/WEEK 12	PLACEBO	203	323.57	86.69	131.0	609.0	203	-2.90	62.95	-268.0	156.0
		SB 207499	436	322.27	80.40	125.0	590.0	433	-4.60	56.25	-225.0	228.0
	VISIT 7/WEEK 16	PLACEBO	194	324.40	87.65	154.0	670.0	194	-0.46	62.24	-272.0	224.0
		SB 207499	426	321.94	77.17	103.0	643.0	423	-3.96	50.61	-236.0	177.0
	VISIT 8/WEEK 20	PLACEBO	193	328.78	85.28	126.0	611.0	193	5.21	54.29	-200.0	200.0
		SB 207499	430	324.39	75.05	64.0	596.0	427	-2.81	51.19	-339.0	169.0
	VISIT 9/WEEK 24	PLACEBO	189	327.66	85.68	116.0	659.0	189	-0.54	52.81	-198.0	203.0
		SB 207499	420	325.08	77.07	112.0	629.0	417	-2.12	54.51	-291.0	250.0
	VISIT 10/WEEK 28	PLACEBO	185	335.68	88.49	162.0	644.0	185	5.98	57.61	-276.0	188.0
		SB 207499	414	325.79	78.88	110.0	652.0	411	-1.53	53.32	-220.0	207.0
	VISIT 11/WEEK 32	PLACEBO	186	329.13	82.00	118.0	624.0	186	0.64	54.66	-219.0	137.0
		SB 207499	412	328.22	79.04	111.0	599.0	409	1.58	56.90	-263.0	229.0
	VISIT 12/WEEK 36	PLACEBO	184	335.69	83.75	120.0	643.0	184	6.93	58.16	-257.0	242.0
		SB 207499	405	326.53	76.82	119.0	563.0	402	-0.49	57.50	-289.0	204.0
	VISIT 13/WEEK 40	PLACEBO	180	336.49	91.72	138.0	835.0	180	7.45	65.10	-247.0	369.0
		SB 207499	397	325.27	78.74	119.0	622.0	394	-1.25	59.95	-286.0	265.0
	VISIT 14/WEEK 44	PLACEBO	180	328.91	83.86	116.0	596.0	180	1.10	64.87	-251.0	146.0
		SB 207499	397	323.26	79.28	136.0	572.0	394	-3.38	60.72	-295.0	201.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Uric Acid (UMOL/L)	VISIT 15/WEEK 48	PLACEBO	180	331.67	82.27	155.0	596.0	180	4.16	59.39	-265.0	178.0
		SB 207499	386	323.28	80.56	106.0	592.0	383	-2.56	61.54	-266.0	238.0
	VISIT 16/WEEK 52	PLACEBO	177	333.32	97.10	147.0	866.0	177	2.81	75.27	-269.0	445.0
		SB 207499	375	321.22	83.61	104.0	633.0	372	-4.31	64.46	-284.0	355.0
	VISIT 17/WEEK 56	PLACEBO	170	326.86	79.46	150.0	594.0	170	-0.76	56.27	-160.0	179.0
		SB 207499	360	317.17	80.74	108.0	616.0	357	-7.69	62.67	-288.0	229.0
	VISIT 18/WEEK 60	PLACEBO	170	325.09	85.72	118.0	584.0	170	-3.13	63.32	-220.0	223.0
		SB 207499	363	316.35	81.99	127.0	673.0	360	-9.46	60.15	-231.0	321.0
	VISIT 19/WEEK 64	PLACEBO	138	325.63	80.79	158.0	555.0	138	3.59	63.25	-246.0	145.0
		SB 207499	299	316.45	81.19	121.0	655.0	296	-4.03	58.04	-237.0	197.0
	VISIT 20/WEEK 68	PLACEBO	135	330.10	85.17	154.0	560.0	135	6.94	63.65	-248.0	196.0
		SB 207499	292	315.75	82.83	108.0	621.0	289	-4.65	58.05	-226.0	190.0
	VISIT 21/WEEK 72	PLACEBO	170	328.36	86.06	143.0	667.0	170	0.84	55.69	-229.0	147.0
		SB 207499	354	324.77	86.27	120.0	626.0	351	-0.89	61.56	-259.0	185.0
	VISIT 22/WEEK 76	PLACEBO	97	330.77	81.68	194.0	615.0	97	14.81	54.38	-116.0	178.0
		SB 207499	196	319.37	90.68	106.0	707.0	194	6.09	64.23	-194.0	373.0
	VISIT 23/WEEK 80	PLACEBO	98	337.58	93.92	187.0	641.0	98	19.19	56.55	-133.0	161.0
		SB 207499	187	324.82	86.39	159.0	696.0	186	14.54	61.07	-160.0	339.0
	VISIT 24/WEEK 84	PLACEBO	159	337.96	82.66	171.0	609.0	159	8.79	60.06	-227.0	194.0
		SB 207499	331	329.92	83.57	152.0	634.0	329	6.26	67.34	-303.0	398.0
	VISIT 25/WEEK 88	PLACEBO	52	339.46	81.82	181.0	541.0	52	22.56	66.40	-190.0	163.0
		SB 207499	97	320.70	73.92	135.0	491.0	96	16.61	53.34	-102.0	179.0
	VISIT 26/WEEK 92	PLACEBO	52	345.56	78.25	212.0	513.0	52	27.50	60.15	-121.0	158.0
		SB 207499	93	327.25	70.67	182.0	499.0	92	21.40	63.19	-205.0	166.0
	VISIT 27/WEEK 96	PLACEBO	159	332.49	79.71	155.0	598.0	159	4.69	65.31	-229.0	172.0
		SB 207499	323	328.04	80.47	127.0	618.0	321	4.76	61.50	-205.0	229.0
	VISIT 28/WEEK 10	PLACEBO	21	370.57	80.99	247.0	532.0	21	59.24	79.25	-104.0	200.0
		SB 207499	49	338.92	76.41	190.0	512.0	49	25.98	59.74	-151.0	135.0
	VISIT 29/WEEK 10	PLACEBO	18	379.39	97.33	233.0	516.0	18	62.94	85.59	-88.0	266.0
		SB 207499	40	343.90	82.04	170.0	529.0	40	35.88	53.71	-90.0	132.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Uric Acid (UMOL/L)	VISIT 30/WEEK 10	PLACEBO	130	331.05	89.07	103.0	644.0	130	6.24	63.38	-246.0	188.0
		SB 207499	270	325.06	80.48	157.0	647.0	268	4.62	64.68	-308.0	181.0
	VISIT 31/WEEK 11	PLACEBO	9	392.22	79.89	243.0	521.0	9	83.33	59.26	3.0	168.0
		SB 207499	18	329.50	84.08	159.0	465.0	18	44.67	54.81	-41.0	169.0
	VISIT 32/WEEK 11	PLACEBO	9	389.78	91.81	229.0	570.0	9	80.89	75.07	-8.0	206.0
		SB 207499	16	330.25	94.97	135.0	486.0	16	47.38	57.63	-5.0	201.0
	VISIT 33/WEEK 12	PLACEBO	88	321.68	80.48	153.0	520.0	88	3.24	69.37	-232.0	195.0
		SB 207499	182	318.75	85.91	142.0	592.0	181	4.37	66.51	-168.0	204.0
	VISIT 34/WEEK 12	PLACEBO	3	338.33	17.47	319.0	353.0	3	41.67	85.47	-57.0	93.0
		SB 207499	3	327.33	79.03	273.0	418.0	3	52.67	95.69	-31.0	157.0
	VISIT 35/WEEK 12	PLACEBO	3	387.33	41.40	355.0	434.0	3	90.67	57.74	24.0	125.0
		SB 207499	3	332.33	99.55	231.0	430.0	3	57.67	34.59	32.0	97.0
	VISIT 36/WEEK 13	PLACEBO	31	312.19	81.02	203.0	546.0	31	24.65	64.54	-72.0	161.0
		SB 207499	58	323.36	79.17	147.0	511.0	57	6.93	65.06	-119.0	177.0
	VISIT 37/WEEK 13	PLACEBO	1	347.00	.	347.0	347.0	1	117.00	.	117.0	117.0
		SB 207499	2	308.50	79.90	252.0	365.0	2	48.50	98.29	-21.0	118.0
	ENDPOINT	PLACEBO	238	322.20	92.27	103.0	866.0	238	-2.83	73.88	-272.0	445.0
		SB 207499	472	321.89	81.00	127.0	613.0	468	-2.96	64.92	-308.0	228.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

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TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Alkaline Phosphatase (IU/L)	BASELINE	PLACEBO	242	74.55	21.99	27.0	158.0	0	.	.	.	.
		SB 207499	476	75.58	21.88	23.0	190.0	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	231	72.65	21.81	29.0	191.0	230	-2.02	12.60	-56.0	42.0
		SB 207499	471	73.78	21.83	23.0	177.0	467	-1.79	11.37	-57.0	51.0
	VISIT 2/WEEK 1	PLACEBO	229	71.40	20.61	25.0	188.0	228	-2.89	11.69	-56.0	35.0
		SB 207499	448	73.39	21.80	29.0	176.0	444	-2.19	11.87	-49.0	50.0
	VISIT 3/WEEK 2	PLACEBO	221	71.75	20.82	22.0	195.0	220	-3.18	12.63	-54.0	40.0
		SB 207499	447	73.82	22.22	34.0	174.0	445	-2.07	13.27	-48.0	113.0
	VISIT 4/WEEK 4	PLACEBO	210	72.50	20.77	28.0	175.0	209	-2.29	12.84	-52.0	42.0
		SB 207499	440	73.74	21.23	28.0	162.0	437	-1.86	11.88	-55.0	71.0
	VISIT 5/WEEK 8	PLACEBO	208	73.33	21.40	25.0	179.0	207	-0.89	13.24	-57.0	47.0
		SB 207499	433	73.29	20.00	20.0	166.0	431	-2.18	10.85	-60.0	36.0
	VISIT 6/WEEK 12	PLACEBO	202	73.97	20.75	32.0	169.0	201	-1.48	13.39	-55.0	38.0
		SB 207499	432	73.39	21.05	24.0	189.0	429	-2.07	12.61	-50.0	97.0
	VISIT 7/WEEK 16	PLACEBO	193	74.58	22.34	31.0	164.0	192	-0.64	13.29	-43.0	41.0
		SB 207499	424	73.37	20.78	30.0	187.0	421	-1.65	11.81	-65.0	48.0
	VISIT 8/WEEK 20	PLACEBO	192	73.47	21.85	32.0	167.0	192	-0.81	12.36	-43.0	33.0
		SB 207499	427	72.93	21.15	29.0	181.0	424	-2.32	11.88	-62.0	37.0
	VISIT 9/WEEK 24	PLACEBO	189	73.37	21.68	29.0	156.0	189	-1.29	13.82	-61.0	59.0
		SB 207499	416	73.20	22.61	27.0	223.0	413	-1.98	13.90	-57.0	134.0
	VISIT 10/WEEK 28	PLACEBO	184	73.09	21.14	27.0	151.0	184	-1.09	13.69	-65.0	50.0
		SB 207499	411	73.26	22.50	30.0	200.0	408	-2.23	13.49	-74.0	75.0
	VISIT 11/WEEK 32	PLACEBO	186	72.06	20.26	24.0	145.0	186	-2.45	13.81	-70.0	45.0
		SB 207499	409	71.87	22.00	17.0	185.0	406	-3.42	13.48	-79.0	102.0
	VISIT 12/WEEK 36	PLACEBO	184	72.04	19.87	26.0	143.0	184	-1.96	14.07	-62.0	43.0
		SB 207499	404	71.84	20.67	30.0	179.0	401	-3.61	12.32	-70.0	42.0
	VISIT 13/WEEK 40	PLACEBO	178	70.94	18.88	26.0	132.0	178	-3.41	14.26	-61.0	26.0
		SB 207499	392	70.99	21.02	30.0	202.0	389	-4.35	12.82	-71.0	40.0
	VISIT 14/WEEK 44	PLACEBO	180	71.83	22.00	27.0	194.0	180	-2.57	17.32	-56.0	128.0
		SB 207499	395	71.96	21.34	29.0	199.0	392	-3.61	14.32	-90.0	95.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Alkaline Phosphatase (IU/L)	VISIT 15/WEEK 48	PLACEBO	180	71.40	20.07	19.0	158.0	180	-2.93	14.05	-58.0	43.0
		SB 207499	384	71.10	19.44	31.0	155.0	381	-3.72	12.78	-77.0	37.0
	VISIT 16/WEEK 52	PLACEBO	177	71.94	20.38	26.0	154.0	177	-2.53	14.98	-65.0	39.0
		SB 207499	371	71.10	19.96	33.0	164.0	368	-3.53	12.81	-86.0	40.0
	VISIT 17/WEEK 56	PLACEBO	165	72.09	20.05	29.0	139.0	165	-2.25	13.39	-40.0	40.0
		SB 207499	355	72.07	22.08	29.0	169.0	352	-2.44	14.39	-88.0	104.0
	VISIT 18/WEEK 60	PLACEBO	169	72.13	19.79	29.0	155.0	169	-1.57	13.88	-50.0	40.0
		SB 207499	361	72.89	21.58	31.0	178.0	358	-2.44	13.50	-80.0	94.0
	VISIT 19/WEEK 64	PLACEBO	138	73.99	20.12	30.0	134.0	138	-2.28	13.01	-54.0	32.0
		SB 207499	296	72.59	19.86	32.0	149.0	293	-2.25	12.71	-72.0	28.0
	VISIT 20/WEEK 68	PLACEBO	135	75.42	21.33	28.0	144.0	135	-1.36	13.02	-33.0	62.0
		SB 207499	292	72.79	19.67	36.0	138.0	289	-2.55	12.82	-64.0	42.0
	VISIT 21/WEEK 72	PLACEBO	170	73.74	19.71	32.0	146.0	170	-0.88	13.42	-45.0	35.0
		SB 207499	352	73.28	20.62	31.0	192.0	349	-0.86	11.62	-38.0	45.0
	VISIT 22/WEEK 76	PLACEBO	97	72.52	20.93	31.0	141.0	97	-3.02	13.76	-53.0	44.0
		SB 207499	196	72.42	19.59	29.0	139.0	194	-1.77	12.60	-81.0	41.0
	VISIT 23/WEEK 80	PLACEBO	98	73.56	19.94	35.0	128.0	98	-1.55	14.05	-50.0	47.0
		SB 207499	187	72.78	19.92	29.0	143.0	186	-1.68	10.77	-40.0	39.0
	VISIT 24/WEEK 84	PLACEBO	159	73.25	19.01	30.0	149.0	159	-0.96	14.55	-66.0	34.0
		SB 207499	330	74.53	21.88	28.0	156.0	328	-0.23	14.23	-56.0	93.0
	VISIT 25/WEEK 88	PLACEBO	52	70.75	15.77	41.0	117.0	52	-2.46	14.87	-70.0	31.0
		SB 207499	97	73.47	23.79	38.0	204.0	96	-0.27	16.23	-70.0	58.0
	VISIT 26/WEEK 92	PLACEBO	52	69.65	17.25	33.0	120.0	52	-2.46	14.61	-74.0	30.0
		SB 207499	93	71.92	18.20	37.0	126.0	92	-1.25	15.03	-82.0	40.0
	VISIT 27/WEEK 96	PLACEBO	159	73.43	18.93	10.0	134.0	159	-1.60	15.78	-69.0	32.0
		SB 207499	322	73.61	22.59	31.0	206.0	320	-0.63	16.34	-78.0	124.0
	VISIT 28/WEEK 10	PLACEBO	21	65.81	18.15	37.0	112.0	21	-3.95	12.82	-26.0	29.0
		SB 207499	49	67.98	19.42	38.0	129.0	49	-4.29	12.38	-45.0	24.0
	VISIT 29/WEEK 10	PLACEBO	18	64.89	17.21	37.0	113.0	18	-2.78	10.72	-17.0	27.0
		SB 207499	40	69.30	17.98	41.0	120.0	40	-2.65	13.07	-41.0	24.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Alkaline Phosphatase (IU/L)	VISIT 30/WEEK 10	PLACEBO	130	73.93	20.53	28.0	149.0	130	-0.64	13.35	-51.0	49.0
		SB 207499	270	74.42	23.73	30.0	209.0	268	-0.47	15.40	-77.0	86.0
	VISIT 31/WEEK 11	PLACEBO	9	56.78	11.63	38.0	77.0	9	-2.00	10.58	-16.0	14.0
		SB 207499	18	65.06	17.38	37.0	101.0	18	-6.00	13.04	-25.0	28.0
	VISIT 32/WEEK 11	PLACEBO	9	58.00	10.30	43.0	73.0	9	-0.78	11.56	-18.0	23.0
		SB 207499	16	67.31	15.70	45.0	97.0	16	-4.13	9.13	-20.0	11.0
	VISIT 33/WEEK 12	PLACEBO	88	75.24	21.09	34.0	171.0	88	-0.42	14.73	-31.0	56.0
		SB 207499	182	73.59	20.37	29.0	157.0	181	-1.60	13.60	-92.0	35.0
	VISIT 34/WEEK 12	PLACEBO	3	58.67	3.79	56.0	63.0	3	9.00	14.73	-8.0	18.0
		SB 207499	3	84.33	28.36	52.0	105.0	3	0.67	1.15	0.0	2.0
	VISIT 35/WEEK 12	PLACEBO	3	59.33	8.08	52.0	68.0	3	9.67	8.33	3.0	19.0
		SB 207499	3	88.67	29.14	56.0	112.0	3	5.00	2.65	2.0	7.0
	VISIT 36/WEEK 13	PLACEBO	30	72.50	15.08	48.0	109.0	30	2.53	13.00	-20.0	31.0
		SB 207499	58	70.00	17.78	38.0	125.0	57	0.44	11.15	-30.0	28.0
	VISIT 37/WEEK 13	PLACEBO	1	52.00	.	52.0	52.0	1	7.00	.	7.0	7.0
		SB 207499	2	92.00	50.91	56.0	128.0	2	19.00	18.38	6.0	32.0
ENDPOINT		PLACEBO	238	74.36	20.22	28.0	171.0	237	0.26	14.84	-72.0	59.0
		SB 207499	472	76.62	23.36	29.0	209.0	468	1.17	16.36	-92.0	94.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Aspartate Aminotransferase (IU/L)	BASELINE	PLACEBO	242	20.80	8.34	9.0	66.0	0	.	.	.	.
		SB 207499	476	20.58	12.35	10.0	225.0	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	232	20.62	9.46	7.0	100.0	231	0.06	8.70	-30.0	53.0
		SB 207499	473	19.52	7.59	8.0	84.0	469	-1.13	12.06	-201.0	67.0
	VISIT 2/WEEK 1	PLACEBO	229	20.28	9.52	9.0	99.0	228	-0.72	8.79	-31.0	74.0
		SB 207499	449	19.39	7.54	5.0	74.0	445	-1.25	11.99	-200.0	50.0
	VISIT 3/WEEK 2	PLACEBO	221	19.81	7.43	9.0	59.0	220	-1.12	7.19	-32.0	34.0
		SB 207499	447	19.67	11.93	8.0	226.0	445	-0.91	15.22	-193.0	210.0
	VISIT 4/WEEK 4	PLACEBO	210	20.31	8.69	11.0	89.0	209	-0.33	7.86	-33.0	42.0
		SB 207499	440	19.61	8.60	9.0	102.0	437	-1.17	12.07	-177.0	83.0
	VISIT 5/WEEK 8	PLACEBO	208	20.13	8.44	8.0	78.0	207	-0.42	6.47	-21.0	24.0
		SB 207499	433	19.31	7.15	10.0	55.0	431	-1.43	11.26	-183.0	38.0
	VISIT 6/WEEK 12	PLACEBO	202	20.05	9.20	9.0	101.0	201	-0.52	8.83	-52.0	80.0
		SB 207499	433	19.40	8.27	7.0	91.0	430	-1.28	12.46	-190.0	61.0
	VISIT 7/WEEK 16	PLACEBO	193	19.67	8.89	3.0	88.0	192	-1.04	7.47	-36.0	45.0
		SB 207499	424	19.68	7.35	7.0	59.0	421	-0.96	10.62	-168.0	31.0
	VISIT 8/WEEK 20	PLACEBO	192	19.36	7.68	7.0	63.0	192	-1.09	5.98	-21.0	20.0
		SB 207499	427	19.39	8.67	8.0	140.0	424	-1.33	12.61	-178.0	119.0
	VISIT 9/WEEK 24	PLACEBO	189	19.04	7.30	10.0	70.0	189	-1.37	7.19	-52.0	27.0
		SB 207499	417	20.08	12.57	8.0	234.0	414	-0.76	15.74	-187.0	213.0
	VISIT 10/WEEK 28	PLACEBO	185	19.86	7.80	9.0	80.0	185	-0.70	7.50	-50.0	37.0
		SB 207499	411	19.84	12.07	8.0	218.0	408	-0.99	8.21	-93.0	68.0
	VISIT 11/WEEK 32	PLACEBO	186	19.76	8.11	8.0	77.0	186	-0.93	7.38	-50.0	34.0
		SB 207499	410	19.46	7.61	8.0	70.0	407	-1.34	11.21	-156.0	41.0
	VISIT 12/WEEK 36	PLACEBO	184	20.03	8.95	10.0	99.0	184	-0.71	7.07	-25.0	33.0
		SB 207499	404	19.54	7.06	8.0	73.0	401	-1.23	12.11	-186.0	43.0
	VISIT 13/WEEK 40	PLACEBO	179	19.84	9.52	10.0	112.0	179	-0.84	8.30	-33.0	65.0
		SB 207499	395	19.90	11.41	9.0	180.0	392	-0.96	12.55	-141.0	139.0
	VISIT 14/WEEK 44	PLACEBO	180	20.49	10.25	10.0	98.0	180	-0.14	9.04	-26.0	55.0
		SB 207499	395	19.99	10.72	9.0	181.0	392	-0.71	8.08	-94.0	36.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Aspartate Aminotransferase (IU/L)	VISIT 15/WEEK 48	PLACEBO	180	20.52	12.00	8.0	109.0	180	-0.14	10.73	-28.0	86.0
		SB 207499	385	19.86	8.30	9.0	91.0	382	-0.90	13.16	-188.0	75.0
	VISIT 16/WEEK 52	PLACEBO	177	20.67	11.67	10.0	92.0	177	-0.11	9.52	-28.0	63.0
		SB 207499	374	19.41	6.72	7.0	50.0	371	-0.94	7.85	-98.0	27.0
	VISIT 17/WEEK 56	PLACEBO	167	20.54	10.14	10.0	86.0	167	0.08	8.57	-24.0	65.0
		SB 207499	358	19.88	9.59	8.0	136.0	355	-0.49	10.68	-98.0	121.0
	VISIT 18/WEEK 60	PLACEBO	170	20.28	8.59	7.0	68.0	170	-0.12	7.76	-27.0	47.0
		SB 207499	362	19.83	9.26	8.0	123.0	359	-1.09	14.13	-189.0	105.0
	VISIT 19/WEEK 64	PLACEBO	138	20.46	10.32	9.0	83.0	138	0.18	8.69	-23.0	43.0
		SB 207499	298	19.37	7.48	9.0	64.0	295	-0.99	8.49	-92.0	40.0
	VISIT 20/WEEK 68	PLACEBO	135	20.73	11.11	6.0	88.0	135	0.39	8.26	-23.0	45.0
		SB 207499	292	19.61	9.56	6.0	115.0	289	-0.88	9.94	-70.0	102.0
	VISIT 21/WEEK 72	PLACEBO	170	20.82	12.07	7.0	100.0	170	0.20	10.15	-29.0	68.0
		SB 207499	352	19.99	10.03	8.0	128.0	349	-0.94	10.09	-97.0	69.0
	VISIT 22/WEEK 76	PLACEBO	97	19.36	5.66	10.0	40.0	97	-1.08	6.36	-28.0	17.0
		SB 207499	196	18.96	6.22	8.0	46.0	194	-1.16	5.60	-24.0	19.0
	VISIT 23/WEEK 80	PLACEBO	98	19.90	7.42	10.0	56.0	98	-0.84	7.04	-26.0	29.0
		SB 207499	187	19.31	7.35	8.0	54.0	186	-0.95	6.81	-24.0	29.0
	VISIT 24/WEEK 84	PLACEBO	159	20.81	11.58	10.0	90.0	159	0.04	8.66	-24.0	47.0
		SB 207499	330	19.99	8.60	8.0	89.0	328	-0.47	10.08	-91.0	72.0
	VISIT 25/WEEK 88	PLACEBO	52	21.17	9.21	9.0	53.0	52	0.38	7.52	-17.0	33.0
		SB 207499	97	18.74	6.52	10.0	59.0	96	-0.61	6.70	-24.0	31.0
	VISIT 26/WEEK 92	PLACEBO	52	20.33	6.79	9.0	41.0	52	-0.58	7.34	-23.0	26.0
		SB 207499	93	19.25	7.42	9.0	60.0	92	0.08	7.38	-23.0	32.0
	VISIT 27/WEEK 96	PLACEBO	159	20.49	10.93	10.0	119.0	159	-0.30	8.67	-25.0	72.0
		SB 207499	322	19.87	9.29	6.0	90.0	320	-0.39	8.43	-40.0	70.0
	VISIT 28/WEEK 10	PLACEBO	21	21.81	8.72	11.0	41.0	21	2.24	6.32	-8.0	15.0
		SB 207499	49	20.31	9.53	8.0	63.0	49	1.04	8.01	-11.0	35.0
	VISIT 29/WEEK 10	PLACEBO	18	20.89	9.66	9.0	52.0	18	0.67	7.16	-9.0	25.0
		SB 207499	40	21.38	8.37	9.0	46.0	40	1.33	7.11	-12.0	23.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Aspartate Aminotransferase (IU/L)	VISIT 30/WEEK 10	PLACEBO	130	21.57	18.73	9.0	202.0	130	0.58	17.51	-22.0	181.0
		SB 207499	270	20.71	9.93	9.0	87.0	268	0.02	9.87	-80.0	62.0
	VISIT 31/WEEK 11	PLACEBO	9	19.44	5.55	12.0	29.0	9	-0.67	3.64	-6.0	5.0
		SB 207499	18	20.11	8.83	10.0	45.0	18	-0.61	4.94	-6.0	15.0
	VISIT 32/WEEK 11	PLACEBO	9	21.44	6.54	13.0	35.0	9	1.33	4.24	-6.0	6.0
		SB 207499	16	21.13	8.64	12.0	42.0	16	0.06	4.99	-9.0	10.0
	VISIT 33/WEEK 12	PLACEBO	88	20.66	9.32	10.0	59.0	88	-0.42	5.82	-24.0	18.0
		SB 207499	182	19.34	6.81	9.0	56.0	181	-1.08	9.86	-93.0	33.0
	VISIT 34/WEEK 12	PLACEBO	3	19.33	3.21	17.0	23.0	3	1.33	4.16	-2.0	6.0
		SB 207499	3	30.33	11.93	22.0	44.0	3	5.00	8.54	-3.0	14.0
	VISIT 35/WEEK 12	PLACEBO	3	19.67	4.04	16.0	24.0	3	1.67	4.73	-2.0	7.0
		SB 207499	3	24.67	7.23	20.0	33.0	3	-0.67	5.51	-7.0	3.0
	VISIT 36/WEEK 13	PLACEBO	30	19.77	6.26	10.0	42.0	30	0.13	6.31	-10.0	21.0
		SB 207499	58	20.21	10.35	9.0	73.0	57	-0.39	8.28	-19.0	36.0
	VISIT 37/WEEK 13	PLACEBO	1	20.00	.	20.0	20.0	1	3.00	.	3.0	3.0
		SB 207499	2	30.00	16.97	18.0	42.0	2	6.00	8.49	0.0	12.0
ENDPOINT		PLACEBO	238	21.01	14.40	9.0	202.0	237	0.15	13.95	-29.0	181.0
		SB 207499	472	20.11	9.38	7.0	87.0	468	-0.54	12.82	-178.0	62.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Alanine Aminotransferase (IU/L)	BASELINE	PLACEBO	242	20.03	13.07	5.0	109.0	0	.	.	.	.
		SB 207499	476	19.83	11.63	6.0	110.0	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	232	20.25	14.97	6.0	142.0	231	0.29	12.01	-43.0	75.0
		SB 207499	473	18.89	11.39	5.0	126.0	469	-1.10	10.44	-94.0	109.0
	VISIT 2/WEEK 1	PLACEBO	229	19.42	13.24	6.0	130.0	228	-0.80	10.35	-46.0	63.0
		SB 207499	450	18.72	10.83	4.0	116.0	446	-1.11	10.33	-96.0	86.0
	VISIT 3/WEEK 2	PLACEBO	221	19.17	11.90	4.0	87.0	220	-1.20	9.18	-46.0	48.0
		SB 207499	447	19.00	18.20	5.0	340.0	445	-0.82	18.57	-95.0	332.0
	VISIT 4/WEEK 4	PLACEBO	212	19.81	14.19	5.0	148.0	211	-0.39	10.84	-45.0	81.0
		SB 207499	440	19.03	11.47	4.0	104.0	437	-1.04	10.30	-81.0	61.0
	VISIT 5/WEEK 8	PLACEBO	208	19.64	11.15	5.0	77.0	207	-0.47	8.94	-46.0	29.0
		SB 207499	433	18.76	10.39	4.0	93.0	431	-1.28	9.75	-79.0	65.0
	VISIT 6/WEEK 12	PLACEBO	202	19.07	11.26	5.0	74.0	201	-1.04	10.13	-65.0	52.0
		SB 207499	433	19.71	14.48	3.0	184.0	430	-0.31	13.56	-86.0	143.0
	VISIT 7/WEEK 16	PLACEBO	193	18.99	12.74	4.0	107.0	192	-1.28	9.91	-63.0	46.0
		SB 207499	425	18.95	10.69	4.0	95.0	422	-1.04	9.35	-66.0	54.0
	VISIT 8/WEEK 20	PLACEBO	192	18.92	12.08	3.0	88.0	192	-1.19	10.23	-67.0	46.0
		SB 207499	427	18.93	10.06	5.0	72.0	424	-1.31	9.34	-70.0	57.0
	VISIT 9/WEEK 24	PLACEBO	189	18.51	11.85	6.0	101.0	189	-1.71	9.45	-59.0	34.0
		SB 207499	417	19.40	11.53	4.0	78.0	414	-0.93	10.46	-87.0	50.0
	VISIT 10/WEEK 28	PLACEBO	185	18.78	10.87	4.0	94.0	185	-1.79	9.69	-68.0	27.0
		SB 207499	411	19.12	13.66	4.0	172.0	408	-1.18	10.74	-77.0	101.0
	VISIT 11/WEEK 32	PLACEBO	186	18.69	11.45	5.0	101.0	186	-1.49	9.78	-67.0	31.0
		SB 207499	410	18.26	10.31	5.0	73.0	407	-2.06	9.95	-78.0	59.0
	VISIT 12/WEEK 36	PLACEBO	184	18.78	10.90	6.0	76.0	184	-1.47	10.46	-68.0	33.0
		SB 207499	404	18.54	9.52	5.0	68.0	401	-1.66	9.91	-82.0	39.0
	VISIT 13/WEEK 40	PLACEBO	179	18.96	13.99	7.0	161.0	179	-1.28	12.34	-78.0	94.0
		SB 207499	395	19.20	13.10	6.0	182.0	392	-1.08	11.19	-76.0	98.0
	VISIT 14/WEEK 44	PLACEBO	180	19.07	12.76	5.0	126.0	180	-1.21	10.99	-76.0	59.0
		SB 207499	395	18.92	12.24	5.0	121.0	392	-1.16	10.56	-80.0	80.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Alanine Aminotransferase (IU/L)	VISIT 15/WEEK 48	PLACEBO	180	19.27	15.43	4.0	152.0	180	-0.88	13.42	-64.0	85.0
		SB 207499	385	18.51	11.09	4.0	113.0	382	-1.57	11.70	-90.0	98.0
	VISIT 16/WEEK 52	PLACEBO	176	20.28	15.43	5.0	141.0	176	-0.19	13.25	-69.0	74.0
		SB 207499	374	18.22	9.54	3.0	72.0	371	-1.67	9.38	-73.0	34.0
	VISIT 17/WEEK 56	PLACEBO	167	19.81	14.14	5.0	133.0	167	-0.40	12.70	-73.0	66.0
		SB 207499	358	19.73	17.38	4.0	279.0	355	-0.23	17.92	-77.0	269.0
	VISIT 18/WEEK 60	PLACEBO	170	19.60	12.52	4.0	84.0	170	-0.62	11.17	-51.0	40.0
		SB 207499	363	18.96	11.65	5.0	126.0	360	-1.24	12.46	-83.0	111.0
	VISIT 19/WEEK 64	PLACEBO	138	19.84	13.58	4.0	91.0	138	-0.58	11.15	-64.0	32.0
		SB 207499	298	18.85	10.86	4.0	90.0	295	-1.36	10.67	-77.0	62.0
	VISIT 20/WEEK 68	PLACEBO	135	20.29	14.37	6.0	96.0	135	-0.21	11.70	-65.0	40.0
		SB 207499	292	19.02	12.18	3.0	95.0	289	-1.41	11.50	-64.0	70.0
	VISIT 21/WEEK 72	PLACEBO	170	19.67	13.91	6.0	114.0	170	-0.65	11.90	-58.0	44.0
		SB 207499	352	19.60	13.11	5.0	130.0	349	-0.67	12.73	-60.0	112.0
	VISIT 22/WEEK 76	PLACEBO	97	18.34	8.65	7.0	53.0	97	-1.29	9.99	-41.0	24.0
		SB 207499	196	18.33	9.95	4.0	77.0	194	-1.46	8.81	-31.0	49.0
	VISIT 23/WEEK 80	PLACEBO	98	18.07	9.96	5.0	65.0	98	-2.03	10.72	-36.0	37.0
		SB 207499	187	18.37	9.76	4.0	63.0	186	-1.56	9.25	-34.0	42.0
	VISIT 24/WEEK 84	PLACEBO	159	19.60	14.08	6.0	119.0	159	-1.11	11.79	-52.0	52.0
		SB 207499	331	18.69	10.52	5.0	82.0	329	-1.57	11.52	-77.0	61.0
	VISIT 25/WEEK 88	PLACEBO	52	20.37	13.45	6.0	69.0	52	0.56	12.59	-29.0	62.0
		SB 207499	97	17.73	7.55	5.0	49.0	96	-1.67	8.46	-24.0	26.0
	VISIT 26/WEEK 92	PLACEBO	52	18.90	10.96	5.0	60.0	52	-0.94	12.07	-35.0	53.0
		SB 207499	93	17.80	8.70	3.0	48.0	92	-1.29	8.89	-28.0	28.0
	VISIT 27/WEEK 96	PLACEBO	159	19.23	14.20	5.0	132.0	159	-1.42	11.47	-54.0	65.0
		SB 207499	322	19.12	13.40	5.0	139.0	320	-0.85	11.71	-33.0	126.0
	VISIT 28/WEEK 10	PLACEBO	21	17.95	11.17	6.0	41.0	21	1.14	9.01	-14.0	19.0
		SB 207499	49	18.43	10.60	7.0	48.0	49	-1.27	8.93	-23.0	25.0
	VISIT 29/WEEK 10	PLACEBO	18	21.67	14.43	6.0	69.0	18	2.17	13.45	-11.0	48.0
		SB 207499	40	19.43	10.08	5.0	56.0	40	-1.58	7.54	-20.0	14.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Alanine Aminotransferase (IU/L)	VISIT 30/WEEK 10	PLACEBO	130	19.98	13.83	4.0	89.0	130	-1.24	12.07	-67.0	50.0
		SB 207499	270	19.89	13.06	7.0	132.0	268	-0.62	12.03	-62.0	97.0
	VISIT 31/WEEK 11	PLACEBO	9	17.67	7.18	10.0	31.0	9	-1.56	6.42	-12.0	6.0
		SB 207499	18	19.06	11.63	8.0	42.0	18	-2.61	5.11	-12.0	6.0
	VISIT 32/WEEK 11	PLACEBO	9	19.67	11.30	7.0	45.0	9	0.44	8.40	-10.0	20.0
		SB 207499	16	19.88	11.32	8.0	47.0	16	-1.88	6.35	-18.0	6.0
	VISIT 33/WEEK 12	PLACEBO	88	21.07	14.52	4.0	86.0	88	-1.20	10.98	-59.0	27.0
		SB 207499	182	18.17	8.50	5.0	62.0	181	-2.16	10.68	-78.0	51.0
	VISIT 34/WEEK 12	PLACEBO	3	21.33	14.43	13.0	38.0	3	3.67	8.96	-2.0	14.0
		SB 207499	3	34.00	21.66	14.0	57.0	3	4.33	16.62	-11.0	22.0
	VISIT 35/WEEK 12	PLACEBO	3	18.67	10.79	11.0	31.0	3	1.00	5.29	-3.0	7.0
		SB 207499	3	31.00	16.52	15.0	48.0	3	1.33	12.58	-12.0	13.0
	VISIT 36/WEEK 13	PLACEBO	30	18.63	9.14	7.0	46.0	30	0.13	9.03	-11.0	35.0
		SB 207499	58	20.93	14.80	8.0	85.0	57	-1.21	15.03	-28.0	75.0
	VISIT 37/WEEK 13	PLACEBO	1	19.00	.	19.0	19.0	1	-5.00	.	-5.0	-5.0
		SB 207499	2	31.50	24.75	14.0	49.0	2	8.00	8.49	2.0	14.0
ENDPOINT		PLACEBO	238	19.76	12.27	4.0	86.0	237	-0.36	11.44	-59.0	48.0
		SB 207499	472	19.42	12.28	3.0	118.0	468	-0.50	13.01	-80.0	102.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Total Bilirubin (UMOL/L)	BASELINE	PLACEBO	243	10.93	3.94	4.0	30.0	0	.	.	.	.
		SB 207499	476	11.09	4.82	0.0	53.0	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	231	11.23	4.42	1.0	28.0	231	0.25	4.15	-24.0	16.0
		SB 207499	468	11.07	4.95	2.0	33.0	464	-0.05	3.98	-24.0	15.0
	VISIT 2/WEEK 1	PLACEBO	230	11.47	4.91	2.0	34.0	230	0.53	4.15	-18.0	23.0
		SB 207499	446	11.08	5.68	0.0	55.0	442	0.02	4.72	-31.0	33.0
	VISIT 3/WEEK 2	PLACEBO	221	11.45	4.84	4.0	37.0	221	0.52	4.60	-18.0	26.0
		SB 207499	445	11.15	5.07	3.0	37.0	443	0.08	3.90	-23.0	16.0
	VISIT 4/WEEK 4	PLACEBO	212	11.22	4.40	1.0	38.0	212	0.39	4.24	-20.0	16.0
		SB 207499	440	11.11	4.83	4.0	33.0	437	-0.03	3.69	-26.0	13.0
	VISIT 5/WEEK 8	PLACEBO	207	11.29	4.51	0.0	44.0	207	0.44	4.22	-19.0	20.0
		SB 207499	433	11.22	5.04	3.0	40.0	431	0.11	4.27	-34.0	17.0
	VISIT 6/WEEK 12	PLACEBO	202	11.41	4.65	4.0	38.0	202	0.58	4.35	-21.0	14.0
		SB 207499	432	11.12	4.91	2.0	32.0	429	-0.07	3.96	-29.0	15.0
	VISIT 7/WEEK 16	PLACEBO	192	10.90	4.40	4.0	32.0	192	0.22	4.19	-14.0	20.0
		SB 207499	424	11.08	5.28	3.0	42.0	421	0.04	4.40	-15.0	35.0
	VISIT 8/WEEK 20	PLACEBO	192	10.76	3.88	4.0	24.0	192	0.03	4.20	-24.0	12.0
		SB 207499	428	11.16	5.22	2.0	38.0	425	0.03	4.16	-24.0	23.0
	VISIT 9/WEEK 24	PLACEBO	188	11.30	4.00	5.0	32.0	188	0.50	3.97	-18.0	13.0
		SB 207499	418	11.54	5.16	2.0	44.0	415	0.34	4.22	-29.0	22.0
	VISIT 10/WEEK 28	PLACEBO	183	11.27	4.37	4.0	27.0	183	0.52	4.60	-21.0	15.0
		SB 207499	411	11.33	4.87	2.0	40.0	408	0.16	4.03	-25.0	20.0
	VISIT 11/WEEK 32	PLACEBO	186	11.31	4.07	4.0	27.0	186	0.56	4.05	-14.0	12.0
		SB 207499	410	11.07	4.77	2.0	34.0	407	0.08	3.95	-11.0	20.0
	VISIT 12/WEEK 36	PLACEBO	184	11.40	4.55	4.0	27.0	184	0.63	4.67	-17.0	16.0
		SB 207499	404	11.07	4.94	3.0	42.0	401	0.03	3.82	-13.0	13.0
	VISIT 13/WEEK 40	PLACEBO	178	11.22	4.70	3.0	31.0	178	0.47	4.82	-20.0	22.0
		SB 207499	392	11.42	5.40	4.0	40.0	389	0.25	4.29	-15.0	26.0
	VISIT 14/WEEK 44	PLACEBO	179	11.27	5.08	0.0	44.0	179	0.61	5.09	-21.0	30.0
		SB 207499	395	11.12	5.37	3.0	44.0	392	-0.05	3.76	-16.0	19.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Total Bilirubin (UMOL/L)	VISIT 15/WEEK 48	PLACEBO	180	10.94	4.27	4.0	30.0	180	0.24	4.43	-23.0	24.0
		SB 207499	384	11.08	5.13	2.0	41.0	381	-0.18	4.27	-28.0	25.0
	VISIT 16/WEEK 52	PLACEBO	177	11.32	8.50	4.0	111.0	177	0.66	8.70	-19.0	102.0
		SB 207499	371	10.81	4.89	3.0	42.0	368	-0.43	4.09	-23.0	20.0
	VISIT 17/WEEK 56	PLACEBO	165	10.62	3.98	3.0	22.0	165	0.03	4.35	-25.0	13.0
		SB 207499	355	10.92	5.59	3.0	48.0	352	-0.38	4.23	-13.0	38.0
	VISIT 18/WEEK 60	PLACEBO	169	10.24	3.97	4.0	28.0	169	-0.35	4.03	-17.0	14.0
		SB 207499	361	10.72	5.00	4.0	49.0	358	-0.54	4.00	-23.0	19.0
	VISIT 19/WEEK 64	PLACEBO	137	10.50	4.57	4.0	34.0	137	-0.06	4.16	-14.0	20.0
		SB 207499	295	10.47	4.84	1.0	36.0	292	-0.78	3.94	-15.0	20.0
	VISIT 20/WEEK 68	PLACEBO	135	10.56	4.04	4.0	27.0	135	0.01	3.88	-16.0	16.0
		SB 207499	291	10.48	4.65	2.0	36.0	288	-0.76	3.86	-20.0	16.0
	VISIT 21/WEEK 72	PLACEBO	169	9.82	3.67	3.0	24.0	169	-0.67	3.70	-19.0	8.0
		SB 207499	350	10.40	4.73	3.0	37.0	347	-0.78	3.97	-28.0	15.0
	VISIT 22/WEEK 76	PLACEBO	97	10.69	5.76	4.0	52.0	97	-0.01	5.65	-16.0	38.0
		SB 207499	196	10.48	4.41	2.0	32.0	194	-1.02	3.93	-21.0	11.0
	VISIT 23/WEEK 80	PLACEBO	98	10.57	5.50	4.0	49.0	98	-0.21	5.32	-16.0	35.0
		SB 207499	187	10.82	5.17	3.0	40.0	186	-0.67	4.30	-14.0	17.0
	VISIT 24/WEEK 84	PLACEBO	159	10.22	3.89	4.0	27.0	159	-0.34	4.17	-18.0	16.0
		SB 207499	329	10.95	5.44	2.0	42.0	327	-0.36	4.02	-13.0	16.0
	VISIT 25/WEEK 88	PLACEBO	52	10.44	4.01	5.0	24.0	52	-1.02	3.77	-15.0	9.0
		SB 207499	97	10.60	4.06	4.0	25.0	96	-0.84	4.01	-11.0	9.0
	VISIT 26/WEEK 92	PLACEBO	52	10.52	4.03	4.0	23.0	52	-0.65	3.71	-7.0	8.0
		SB 207499	93	10.80	4.64	5.0	35.0	92	-0.62	4.25	-11.0	14.0
	VISIT 27/WEEK 96	PLACEBO	158	10.26	4.07	3.0	25.0	158	-0.30	4.26	-17.0	14.0
		SB 207499	321	10.59	4.71	3.0	34.0	319	-0.71	3.82	-24.0	13.0
	VISIT 28/WEEK 10	PLACEBO	21	12.00	3.92	7.0	24.0	21	0.81	4.35	-4.0	15.0
		SB 207499	49	11.41	4.99	5.0	31.0	49	-0.16	5.53	-18.0	13.0
	VISIT 29/WEEK 10	PLACEBO	18	11.61	4.46	6.0	20.0	18	0.11	3.38	-4.0	10.0
		SB 207499	40	10.35	4.12	4.0	27.0	40	-0.83	3.86	-11.0	8.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Total Bilirubin (UMOL/L)	VISIT 30/WEEK 10	PLACEBO	129	10.15	4.47	3.0	33.0	129	-0.36	4.93	-22.0	22.0
		SB 207499	269	10.83	5.08	4.0	31.0	267	-0.71	4.08	-23.0	15.0
	VISIT 31/WEEK 11	PLACEBO	9	12.22	3.73	6.0	18.0	9	0.00	5.05	-7.0	8.0
		SB 207499	18	10.39	5.68	4.0	30.0	18	-2.72	4.64	-16.0	6.0
	VISIT 32/WEEK 11	PLACEBO	9	14.44	4.28	9.0	21.0	9	2.22	4.21	-2.0	11.0
		SB 207499	16	12.13	6.28	7.0	32.0	16	-0.94	4.81	-13.0	8.0
	VISIT 33/WEEK 12	PLACEBO	88	10.40	4.28	3.0	24.0	88	-0.38	4.44	-14.0	14.0
		SB 207499	182	10.81	4.73	4.0	30.0	181	-0.31	4.08	-14.0	13.0
	VISIT 34/WEEK 12	PLACEBO	3	12.00	1.73	10.0	13.0	3	2.00	2.65	-1.0	4.0
		SB 207499	3	11.67	2.52	9.0	14.0	3	-1.67	2.31	-3.0	1.0
	VISIT 35/WEEK 12	PLACEBO	3	22.33	23.09	9.0	49.0	3	12.33	22.23	-1.0	38.0
		SB 207499	3	9.67	2.52	7.0	12.0	3	-3.67	2.31	-5.0	-1.0
	VISIT 36/WEEK 13	PLACEBO	30	11.37	4.61	5.0	22.0	30	-0.30	3.97	-11.0	10.0
		SB 207499	58	10.22	5.21	4.0	37.0	57	-1.67	3.89	-11.0	13.0
	VISIT 37/WEEK 13	PLACEBO	1	10.00	.	10.0	10.0	1	-1.00	.	-1.0	-1.0
		SB 207499	2	7.50	0.71	7.0	8.0	2	-4.00	5.66	-8.0	0.0
	ENDPOINT	PLACEBO	238	11.07	5.31	4.0	42.0	238	0.11	4.64	-22.0	17.0
		SB 207499	472	10.83	4.86	2.0	37.0	468	-0.29	4.18	-23.0	14.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Total Protein (G/L)	BASELINE	PLACEBO	243	70.55	4.35	59.0	83.0	0	.	.	.	.
		SB 207499	476	70.91	4.61	60.0	94.0	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	233	70.77	4.59	59.0	91.0	233	0.24	4.21	-16.0	14.0
		SB 207499	468	70.53	4.41	58.0	87.0	464	-0.44	3.83	-24.0	10.0
	VISIT 2/WEEK 1	PLACEBO	231	70.64	3.95	58.0	81.0	231	0.09	3.85	-11.0	10.0
		SB 207499	447	70.29	4.21	58.0	85.0	443	-0.64	4.00	-26.0	10.0
	VISIT 3/WEEK 2	PLACEBO	221	70.70	4.05	61.0	82.0	221	0.20	4.00	-16.0	9.0
		SB 207499	449	70.37	4.26	57.0	85.0	447	-0.55	3.96	-24.0	10.0
	VISIT 4/WEEK 4	PLACEBO	212	70.85	4.28	61.0	82.0	212	0.37	3.81	-13.0	10.0
		SB 207499	443	70.23	4.26	57.0	83.0	440	-0.60	3.92	-22.0	12.0
	VISIT 5/WEEK 8	PLACEBO	208	70.81	4.23	62.0	83.0	208	0.53	4.13	-13.0	12.0
		SB 207499	436	70.46	4.21	59.0	86.0	433	-0.47	3.89	-19.0	12.0
	VISIT 6/WEEK 12	PLACEBO	203	70.91	4.51	58.0	87.0	203	0.53	4.05	-17.0	11.0
		SB 207499	435	70.57	4.51	60.0	86.0	432	-0.38	4.17	-16.0	20.0
	VISIT 7/WEEK 16	PLACEBO	193	70.80	4.35	59.0	84.0	193	0.35	3.89	-16.0	11.0
		SB 207499	425	70.39	4.30	60.0	83.0	422	-0.47	3.91	-21.0	11.0
	VISIT 8/WEEK 20	PLACEBO	193	70.68	4.49	56.0	82.0	193	0.30	4.05	-16.0	9.0
		SB 207499	429	70.44	4.25	58.0	83.0	426	-0.40	3.69	-22.0	9.0
	VISIT 9/WEEK 24	PLACEBO	188	70.94	4.51	58.0	85.0	188	0.57	3.96	-17.0	10.0
		SB 207499	420	70.89	4.44	61.0	91.0	417	0.05	3.75	-22.0	12.0
	VISIT 10/WEEK 28	PLACEBO	183	71.20	4.61	55.0	82.0	183	0.87	4.28	-17.0	14.0
		SB 207499	414	70.72	4.63	58.0	89.0	411	-0.27	4.19	-25.0	11.0
	VISIT 11/WEEK 32	PLACEBO	186	70.65	4.65	56.0	84.0	186	0.22	4.30	-16.0	12.0
		SB 207499	412	70.71	4.34	58.0	87.0	409	-0.19	3.80	-23.0	11.0
	VISIT 12/WEEK 36	PLACEBO	184	70.68	4.75	52.0	89.0	184	0.29	4.60	-15.0	15.0
		SB 207499	405	70.44	4.41	59.0	86.0	402	-0.51	4.09	-23.0	11.0
	VISIT 13/WEEK 40	PLACEBO	179	70.59	4.11	56.0	83.0	179	0.28	4.04	-12.0	12.0
		SB 207499	393	70.21	4.23	59.0	81.0	390	-0.74	3.95	-22.0	13.0
	VISIT 14/WEEK 44	PLACEBO	180	70.23	4.28	55.0	83.0	180	-0.14	4.24	-15.0	10.0
		SB 207499	397	70.22	4.33	57.0	82.0	394	-0.64	3.87	-24.0	11.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Total Protein (G/L)	VISIT 15/WEEK 48	PLACEBO	180	70.44	4.53	53.0	83.0	180	-0.07	4.43	-17.0	10.0
		SB 207499	385	70.48	4.22	60.0	85.0	382	-0.39	4.05	-26.0	12.0
	VISIT 16/WEEK 52	PLACEBO	177	70.55	4.49	52.0	82.0	177	0.14	4.10	-15.0	11.0
		SB 207499	372	70.21	4.45	58.0	87.0	369	-0.53	3.93	-15.0	12.0
	VISIT 17/WEEK 56	PLACEBO	168	70.36	4.18	60.0	83.0	168	-0.23	4.31	-14.0	12.0
		SB 207499	357	70.30	4.43	58.0	87.0	354	-0.69	3.97	-22.0	8.0
	VISIT 18/WEEK 60	PLACEBO	169	70.34	4.28	60.0	81.0	169	-0.25	4.15	-14.0	10.0
		SB 207499	361	70.11	4.34	57.0	83.0	358	-0.86	3.90	-21.0	9.0
	VISIT 19/WEEK 64	PLACEBO	137	70.41	4.41	57.0	82.0	137	-0.26	4.07	-12.0	10.0
		SB 207499	296	70.31	4.28	58.0	88.0	293	-0.62	3.94	-23.0	12.0
	VISIT 20/WEEK 68	PLACEBO	135	70.51	4.34	56.0	82.0	135	-0.16	4.35	-14.0	10.0
		SB 207499	291	70.04	4.41	57.0	83.0	288	-0.83	4.08	-21.0	11.0
	VISIT 21/WEEK 72	PLACEBO	169	70.08	4.30	56.0	82.0	169	-0.57	4.02	-13.0	11.0
		SB 207499	351	70.09	4.43	55.0	84.0	348	-0.82	4.03	-24.0	10.0
	VISIT 22/WEEK 76	PLACEBO	97	69.97	4.14	59.0	81.0	97	-0.11	4.24	-14.0	11.0
		SB 207499	196	69.45	4.59	57.0	82.0	194	-1.12	4.36	-24.0	9.0
	VISIT 23/WEEK 80	PLACEBO	98	69.68	4.21	58.0	84.0	98	-0.57	4.64	-18.0	8.0
		SB 207499	187	69.52	4.42	51.0	82.0	186	-1.01	4.22	-20.0	10.0
	VISIT 24/WEEK 84	PLACEBO	159	69.77	4.23	61.0	85.0	159	-0.81	4.47	-15.0	10.0
		SB 207499	329	69.84	4.40	60.0	86.0	327	-1.06	4.01	-21.0	13.0
	VISIT 25/WEEK 88	PLACEBO	52	69.42	4.50	54.0	80.0	52	-0.60	4.18	-13.0	8.0
		SB 207499	97	69.46	3.89	58.0	78.0	96	-1.40	4.46	-25.0	10.0
	VISIT 26/WEEK 92	PLACEBO	52	68.96	4.52	58.0	83.0	52	-1.00	4.61	-10.0	13.0
		SB 207499	93	69.57	3.89	62.0	78.0	92	-1.30	4.31	-23.0	9.0
	VISIT 27/WEEK 96	PLACEBO	158	69.91	4.19	60.0	82.0	158	-0.81	4.58	-17.0	12.0
		SB 207499	322	69.27	4.37	57.0	82.0	320	-1.55	4.11	-15.0	11.0
	VISIT 28/WEEK 10	PLACEBO	21	70.81	3.88	61.0	77.0	21	0.10	3.71	-9.0	5.0
		SB 207499	49	69.53	4.15	61.0	80.0	49	-1.31	4.20	-14.0	7.0
	VISIT 29/WEEK 10	PLACEBO	18	70.78	4.05	62.0	77.0	18	0.78	3.75	-8.0	5.0
		SB 207499	40	69.18	4.67	60.0	76.0	40	-1.50	4.55	-16.0	8.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Total Protein (G/L)	VISIT 30/WEEK 10	PLACEBO	129	70.01	4.32	56.0	82.0	129	-0.76	4.31	-13.0	10.0
		SB 207499	269	69.46	4.50	58.0	86.0	267	-1.50	4.62	-24.0	11.0
	VISIT 31/WEEK 11	PLACEBO	9	69.89	2.67	67.0	75.0	9	0.22	1.86	-2.0	3.0
		SB 207499	18	69.50	4.87	60.0	77.0	18	-0.89	4.11	-6.0	8.0
	VISIT 32/WEEK 11	PLACEBO	9	71.44	2.70	68.0	75.0	9	1.78	1.64	0.0	5.0
		SB 207499	16	69.38	4.95	61.0	78.0	16	-0.88	3.58	-6.0	5.0
	VISIT 33/WEEK 12	PLACEBO	88	69.01	4.91	53.0	79.0	88	-1.76	4.73	-17.0	7.0
		SB 207499	182	69.06	4.26	60.0	88.0	181	-1.78	4.31	-13.0	19.0
	VISIT 34/WEEK 12	PLACEBO	3	70.33	3.79	66.0	73.0	3	2.00	5.29	-4.0	6.0
		SB 207499	3	70.67	2.89	69.0	74.0	3	0.00	1.00	-1.0	1.0
	VISIT 35/WEEK 12	PLACEBO	3	69.33	2.52	67.0	72.0	3	1.00	3.61	-3.0	4.0
		SB 207499	3	71.00	2.65	69.0	74.0	3	0.33	0.58	0.0	1.0
	VISIT 36/WEEK 13	PLACEBO	31	69.77	4.63	60.0	80.0	31	-0.23	4.60	-10.0	8.0
		SB 207499	58	68.60	4.34	60.0	77.0	57	-2.44	4.78	-26.0	7.0
	VISIT 37/WEEK 13	PLACEBO	1	67.00	.	67.0	67.0	1	-1.00	.	-1.0	-1.0
		SB 207499	2	71.50	0.71	71.0	72.0	2	0.50	2.12	-1.0	2.0
	ENDPOINT	PLACEBO	238	69.76	4.41	53.0	82.0	238	-0.76	4.31	-17.0	10.0
		SB 207499	472	69.14	4.39	57.0	86.0	468	-1.76	4.28	-26.0	10.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Albumin (G/L)	BASELINE	PLACEBO	243	42.60	2.10	37.0	49.0	0	.	.	.	.
		SB 207499	476	42.81	2.09	36.0	49.0	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	232	42.33	2.28	35.0	52.0	232	-0.23	2.20	-7.0	6.0
		SB 207499	466	42.30	2.17	36.0	49.0	462	-0.59	2.24	-7.0	7.0
	VISIT 2/WEEK 1	PLACEBO	231	42.40	2.23	35.0	49.0	231	-0.22	2.15	-7.0	5.0
		SB 207499	447	42.05	2.20	27.0	50.0	443	-0.77	2.40	-21.0	6.0
	VISIT 3/WEEK 2	PLACEBO	221	42.32	2.24	35.0	49.0	221	-0.29	2.21	-7.0	5.0
		SB 207499	449	42.05	2.01	36.0	48.0	447	-0.76	2.15	-7.0	6.0
	VISIT 4/WEEK 4	PLACEBO	212	42.31	2.07	37.0	48.0	212	-0.26	2.13	-7.0	5.0
		SB 207499	443	41.80	2.09	35.0	48.0	440	-0.99	2.22	-8.0	7.0
	VISIT 5/WEEK 8	PLACEBO	207	41.97	2.13	33.0	49.0	207	-0.56	2.05	-9.0	4.0
		SB 207499	436	41.68	1.97	36.0	49.0	433	-1.12	2.02	-7.0	6.0
	VISIT 6/WEEK 12	PLACEBO	203	41.78	2.23	34.0	51.0	203	-0.77	2.15	-10.0	5.0
		SB 207499	435	41.39	2.13	27.0	47.0	432	-1.41	2.14	-13.0	4.0
	VISIT 7/WEEK 16	PLACEBO	193	41.42	2.16	34.0	47.0	193	-1.12	2.10	-10.0	6.0
		SB 207499	425	41.22	1.91	35.0	47.0	422	-1.57	2.00	-9.0	5.0
	VISIT 8/WEEK 20	PLACEBO	193	41.34	2.22	33.0	46.0	193	-1.21	2.27	-12.0	6.0
		SB 207499	429	41.19	1.86	33.0	46.0	426	-1.62	1.99	-8.0	3.0
	VISIT 9/WEEK 24	PLACEBO	188	41.36	2.33	33.0	49.0	188	-1.17	2.19	-11.0	6.0
		SB 207499	419	41.35	1.91	36.0	48.0	416	-1.48	1.91	-7.0	5.0
	VISIT 10/WEEK 28	PLACEBO	182	41.61	2.24	34.0	49.0	182	-0.95	2.22	-11.0	5.0
		SB 207499	414	41.24	2.02	28.0	47.0	411	-1.64	2.19	-18.0	5.0
	VISIT 11/WEEK 32	PLACEBO	186	41.12	2.37	33.0	49.0	186	-1.45	2.20	-10.0	6.0
		SB 207499	411	41.25	1.88	33.0	46.0	408	-1.59	1.97	-11.0	7.0
	VISIT 12/WEEK 36	PLACEBO	183	41.25	2.27	33.0	49.0	183	-1.31	2.17	-9.0	4.0
		SB 207499	404	41.18	2.02	34.0	48.0	401	-1.66	2.02	-8.0	5.0
	VISIT 13/WEEK 40	PLACEBO	178	41.40	1.97	35.0	47.0	178	-1.17	2.01	-8.0	7.0
		SB 207499	392	41.09	2.00	35.0	49.0	389	-1.74	1.96	-8.0	6.0
	VISIT 14/WEEK 44	PLACEBO	179	41.20	2.18	34.0	48.0	179	-1.40	2.02	-9.0	4.0
		SB 207499	397	41.21	1.98	34.0	46.0	394	-1.59	1.86	-9.0	4.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

SB 207499

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Albumin (G/L)	VISIT 15/WEEK 48	PLACEBO	180	41.46	2.24	34.0	47.0	180	-1.16	2.16	-9.0	5.0
		SB 207499	384	41.49	1.93	35.0	48.0	381	-1.32	1.92	-10.0	4.0
	VISIT 16/WEEK 52	PLACEBO	177	41.80	2.18	32.0	47.0	177	-0.79	2.09	-11.0	4.0
		SB 207499	372	41.65	1.88	36.0	48.0	369	-1.09	2.00	-10.0	5.0
	VISIT 17/WEEK 56	PLACEBO	168	41.82	1.99	37.0	47.0	168	-0.84	2.05	-7.0	5.0
		SB 207499	356	41.76	2.01	35.0	48.0	353	-1.08	2.02	-9.0	4.0
	VISIT 18/WEEK 60	PLACEBO	169	41.90	2.07	37.0	48.0	169	-0.78	2.03	-7.0	4.0
		SB 207499	361	41.78	1.94	36.0	47.0	358	-1.08	1.89	-9.0	5.0
	VISIT 19/WEEK 64	PLACEBO	137	41.99	2.31	35.0	47.0	137	-0.68	2.08	-7.0	4.0
		SB 207499	296	41.85	1.97	36.0	48.0	293	-0.88	1.97	-9.0	6.0
	VISIT 20/WEEK 68	PLACEBO	135	41.90	2.22	36.0	50.0	135	-0.76	2.15	-7.0	5.0
		SB 207499	291	41.71	2.06	36.0	48.0	288	-1.03	2.05	-8.0	6.0
	VISIT 21/WEEK 72	PLACEBO	168	41.87	2.13	34.0	47.0	168	-0.79	2.13	-9.0	6.0
		SB 207499	352	41.86	2.09	36.0	48.0	349	-1.00	2.04	-8.0	6.0
	VISIT 22/WEEK 76	PLACEBO	97	42.07	2.00	37.0	48.0	97	-0.33	2.22	-6.0	5.0
		SB 207499	196	41.53	2.16	35.0	47.0	194	-1.16	2.11	-9.0	4.0
	VISIT 23/WEEK 80	PLACEBO	98	41.77	2.14	36.0	47.0	98	-0.71	2.20	-8.0	4.0
		SB 207499	187	41.55	2.01	33.0	46.0	186	-1.15	1.96	-10.0	4.0
	VISIT 24/WEEK 84	PLACEBO	159	42.09	2.36	37.0	50.0	159	-0.59	2.21	-6.0	6.0
		SB 207499	329	41.95	2.11	35.0	48.0	327	-0.93	1.94	-7.0	5.0
	VISIT 25/WEEK 88	PLACEBO	52	41.54	2.28	36.0	46.0	52	-0.90	2.18	-7.0	4.0
		SB 207499	97	41.90	1.87	37.0	48.0	96	-1.21	1.91	-8.0	4.0
	VISIT 26/WEEK 92	PLACEBO	52	41.40	2.44	34.0	47.0	52	-1.00	2.12	-6.0	5.0
		SB 207499	93	42.10	1.98	36.0	47.0	92	-0.99	1.91	-7.0	4.0
	VISIT 27/WEEK 96	PLACEBO	158	42.36	2.06	36.0	48.0	158	-0.34	2.10	-8.0	6.0
		SB 207499	322	42.02	2.01	37.0	49.0	320	-0.86	2.13	-7.0	5.0
	VISIT 28/WEEK 10	PLACEBO	21	42.43	2.48	37.0	46.0	21	0.05	2.06	-3.0	5.0
		SB 207499	49	42.27	1.90	39.0	47.0	49	-0.57	2.10	-4.0	3.0
	VISIT 29/WEEK 10	PLACEBO	18	42.61	2.50	36.0	47.0	18	0.39	1.69	-3.0	3.0
		SB 207499	40	42.23	1.99	38.0	48.0	40	-0.68	2.40	-8.0	3.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Albumin (G/L)	VISIT 30/WEEK 10	PLACEBO	129	42.41	2.20	36.0	47.0	129	-0.15	2.11	-7.0	5.0
		SB 207499	269	42.22	2.10	36.0	48.0	267	-0.56	2.26	-10.0	6.0
	VISIT 31/WEEK 11	PLACEBO	9	42.44	1.42	40.0	44.0	9	-0.33	1.50	-3.0	2.0
		SB 207499	18	42.50	2.04	39.0	46.0	18	-0.56	1.85	-4.0	3.0
	VISIT 32/WEEK 11	PLACEBO	9	43.22	1.39	41.0	45.0	9	0.44	1.24	-1.0	3.0
		SB 207499	16	42.38	2.19	38.0	47.0	16	-0.50	1.86	-3.0	3.0
	VISIT 33/WEEK 12	PLACEBO	88	42.33	2.47	34.0	47.0	88	-0.33	1.96	-8.0	4.0
		SB 207499	182	42.17	2.33	37.0	53.0	181	-0.36	2.26	-6.0	10.0
	VISIT 34/WEEK 12	PLACEBO	3	44.00	3.46	40.0	46.0	3	0.67	2.31	-2.0	2.0
		SB 207499	3	43.00	2.00	41.0	45.0	3	1.00	1.73	0.0	3.0
	VISIT 35/WEEK 12	PLACEBO	3	42.00	3.61	38.0	45.0	3	-1.33	2.52	-4.0	1.0
		SB 207499	3	43.00	1.73	41.0	44.0	3	1.00	1.00	0.0	2.0
	VISIT 36/WEEK 13	PLACEBO	31	42.81	2.09	38.0	47.0	31	0.00	1.86	-4.0	4.0
		SB 207499	58	42.00	1.95	38.0	47.0	57	-0.84	2.09	-8.0	3.0
	VISIT 37/WEEK 13	PLACEBO	1	44.00	.	44.0	44.0	1	0.00	.	0.0	0.0
		SB 207499	2	44.00	1.41	43.0	45.0	2	1.50	2.12	0.0	3.0
	ENDPOINT	PLACEBO	238	42.15	2.38	33.0	49.0	238	-0.46	2.10	-8.0	5.0
		SB 207499	472	41.74	2.16	33.0	49.0	468	-1.08	2.24	-9.0	7.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Glucose - Random (MMOL/L)	BASELINE	PLACEBO	242	6.11	1.88	3.4	19.7	0	.	.	.	.
		SB 207499	476	6.09	2.24	2.3	23.3	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	232	6.25	2.08	3.0	18.2	231	0.13	1.53	-4.5	5.4
		SB 207499	468	6.19	2.07	2.1	19.1	464	0.09	1.75	-13.3	7.6
	VISIT 2/WEEK 1	PLACEBO	230	6.37	1.99	3.4	17.4	229	0.23	1.56	-6.3	5.3
		SB 207499	447	6.18	2.06	1.9	19.6	443	0.08	1.91	-12.6	14.6
	VISIT 3/WEEK 2	PLACEBO	221	6.25	2.09	3.4	24.6	220	0.13	1.68	-6.2	6.0
		SB 207499	450	6.14	1.86	2.4	18.2	448	0.04	1.88	-15.4	5.8
	VISIT 4/WEEK 4	PLACEBO	210	6.20	1.61	3.7	14.0	209	0.08	1.54	-5.7	4.7
		SB 207499	443	6.20	1.96	2.8	18.8	440	0.14	1.70	-8.3	6.8
	VISIT 5/WEEK 8	PLACEBO	208	6.30	1.92	3.5	23.6	207	0.17	1.47	-4.7	4.7
		SB 207499	436	6.20	2.17	2.7	19.9	433	0.10	1.70	-10.7	10.3
	VISIT 6/WEEK 12	PLACEBO	203	6.26	1.95	1.1	19.8	202	0.13	1.56	-4.7	8.3
		SB 207499	435	6.27	2.44	2.3	26.8	432	0.16	1.97	-14.9	12.9
	VISIT 7/WEEK 16	PLACEBO	194	6.25	1.89	3.3	20.8	193	0.16	1.62	-4.3	6.3
		SB 207499	424	6.32	2.14	2.9	20.4	421	0.23	1.88	-15.0	10.5
	VISIT 8/WEEK 20	PLACEBO	193	6.31	2.01	3.8	19.8	193	0.17	1.48	-4.0	6.5
		SB 207499	428	6.24	2.08	1.5	19.4	425	0.14	1.71	-14.9	8.6
	VISIT 9/WEEK 24	PLACEBO	188	6.35	2.21	3.4	21.8	188	0.18	1.62	-5.9	5.0
		SB 207499	418	6.19	2.28	2.3	26.2	415	0.06	1.78	-12.9	7.9
	VISIT 10/WEEK 28	PLACEBO	182	6.44	2.12	3.6	20.5	182	0.26	1.70	-5.1	6.7
		SB 207499	414	6.33	2.39	2.5	23.4	411	0.23	1.94	-13.4	11.9
	VISIT 11/WEEK 32	PLACEBO	186	6.42	2.12	3.3	18.2	186	0.27	1.73	-5.6	10.9
		SB 207499	411	6.26	2.25	1.4	21.6	408	0.13	1.89	-12.8	12.0
	VISIT 12/WEEK 36	PLACEBO	183	6.31	2.11	1.3	18.9	183	0.14	1.76	-5.8	6.4
		SB 207499	404	6.25	2.13	3.0	20.9	401	0.11	1.96	-13.7	7.7
	VISIT 13/WEEK 40	PLACEBO	178	6.39	2.25	3.1	19.3	178	0.24	1.75	-6.2	5.9
		SB 207499	392	6.37	2.31	2.2	21.1	389	0.23	1.83	-12.3	10.3
	VISIT 14/WEEK 44	PLACEBO	179	6.53	2.24	3.8	20.4	179	0.37	1.72	-4.4	7.3
		SB 207499	397	6.35	2.20	1.9	20.0	394	0.20	1.91	-13.2	8.6

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Glucose - Random (MMOL/L)	VISIT 15/WEEK 48	PLACEBO	180	6.19	1.96	2.9	18.7	180	0.03	1.75	-6.4	6.3
		SB 207499	384	6.24	2.27	2.7	22.1	381	0.08	1.98	-14.6	11.3
	VISIT 16/WEEK 52	PLACEBO	177	6.46	2.04	3.9	18.2	177	0.28	1.71	-4.2	5.2
		SB 207499	372	6.29	2.13	2.7	17.5	369	0.14	1.84	-13.7	10.0
	VISIT 17/WEEK 56	PLACEBO	168	6.34	2.03	2.6	19.1	168	0.11	1.84	-5.4	8.9
		SB 207499	356	6.14	2.12	2.6	22.0	353	0.06	1.90	-12.9	11.2
	VISIT 18/WEEK 60	PLACEBO	169	6.21	1.94	3.4	19.0	169	-0.01	1.62	-4.7	4.8
		SB 207499	360	6.22	2.14	1.5	19.1	357	0.09	1.98	-11.1	9.4
	VISIT 19/WEEK 64	PLACEBO	137	6.16	1.64	3.3	12.9	137	0.09	1.60	-4.3	4.8
		SB 207499	296	6.22	1.98	2.5	16.6	293	-0.01	1.96	-11.4	7.8
	VISIT 20/WEEK 68	PLACEBO	134	6.23	1.46	2.8	11.3	134	0.13	1.75	-4.8	6.3
		SB 207499	291	6.23	2.10	3.1	18.6	288	0.00	1.96	-13.3	7.8
	VISIT 21/WEEK 72	PLACEBO	168	6.22	1.83	3.9	19.7	168	0.04	1.62	-5.2	5.4
		SB 207499	352	6.09	1.82	2.6	15.9	349	-0.05	2.01	-11.1	8.2
	VISIT 22/WEEK 76	PLACEBO	97	6.25	1.75	4.1	14.5	97	0.18	1.64	-5.3	4.6
		SB 207499	196	6.43	2.29	3.1	18.5	194	0.09	1.95	-10.8	12.4
	VISIT 23/WEEK 80	PLACEBO	98	6.35	1.84	4.0	14.7	98	0.31	1.80	-4.5	7.1
		SB 207499	187	6.40	2.25	3.1	20.2	186	0.06	2.23	-11.0	14.3
	VISIT 24/WEEK 84	PLACEBO	158	6.31	1.92	3.6	14.4	158	0.13	1.83	-5.5	5.4
		SB 207499	329	6.20	1.94	2.4	19.0	327	0.01	1.98	-10.7	8.2
	VISIT 25/WEEK 88	PLACEBO	52	6.17	1.55	4.2	13.9	52	-0.05	1.53	-4.7	3.2
		SB 207499	97	5.81	1.46	2.5	12.2	96	-0.16	1.82	-11.8	3.8
	VISIT 26/WEEK 92	PLACEBO	52	6.68	2.39	4.2	16.2	52	0.56	1.91	-3.6	7.0
		SB 207499	93	6.11	1.77	3.6	14.5	92	0.14	2.11	-10.1	8.6
	VISIT 27/WEEK 96	PLACEBO	158	6.23	1.74	3.0	15.6	158	0.04	1.64	-4.9	5.0
		SB 207499	322	6.35	2.41	3.4	29.0	320	0.16	2.10	-12.7	10.0
	VISIT 28/WEEK 10	PLACEBO	21	6.22	1.51	4.3	11.7	21	-0.14	1.67	-5.0	2.3
		SB 207499	49	6.29	1.37	4.0	12.1	49	0.16	1.33	-3.0	3.4
	VISIT 29/WEEK 10	PLACEBO	18	6.47	1.97	4.3	11.4	18	0.09	1.58	-3.5	3.5
		SB 207499	40	6.27	1.66	3.9	13.3	40	0.30	1.32	-1.7	4.6

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Glucose - Random (MMOL/L)	VISIT 30/WEEK 10	PLACEBO	129	6.47	1.89	4.4	14.1	129	0.23	1.80	-6.2	6.5
		SB 207499	269	6.10	1.72	2.7	15.4	267	-0.06	1.85	-11.9	6.3
	VISIT 31/WEEK 11	PLACEBO	9	6.70	1.83	5.0	11.1	9	0.24	1.62	-3.6	2.2
		SB 207499	18	6.27	1.31	4.4	9.0	18	0.01	1.34	-2.4	3.2
	VISIT 32/WEEK 11	PLACEBO	9	6.53	1.76	5.4	11.0	9	0.08	1.29	-2.9	1.5
		SB 207499	16	6.31	1.66	4.5	10.9	16	0.42	1.94	-2.1	5.0
	VISIT 33/WEEK 12	PLACEBO	88	6.58	1.86	4.3	14.0	88	0.41	1.88	-5.2	6.4
		SB 207499	182	6.26	2.00	2.4	14.8	181	-0.06	1.88	-10.5	4.7
	VISIT 34/WEEK 12	PLACEBO	3	5.97	0.57	5.5	6.6	3	1.00	0.90	0.1	1.9
		SB 207499	3	8.10	2.07	6.2	10.3	3	2.13	2.80	-1.0	4.4
	VISIT 35/WEEK 12	PLACEBO	3	5.93	1.18	5.2	7.3	3	0.97	1.44	-0.1	2.6
		SB 207499	3	9.10	4.33	6.5	14.1	3	3.13	4.52	-0.5	8.2
	VISIT 36/WEEK 13	PLACEBO	31	5.86	1.18	4.6	9.7	31	0.43	1.19	-1.9	3.4
		SB 207499	58	6.38	2.44	3.6	15.7	57	0.24	2.23	-4.5	9.8
	VISIT 37/WEEK 13	PLACEBO	1	5.60	.	5.6	5.6	1	0.90	.	0.9	0.9
		SB 207499	2	6.80	1.84	5.5	8.1	2	1.45	1.06	0.7	2.2
	ENDPOINT	PLACEBO	238	6.28	1.95	3.4	19.8	237	0.16	1.86	-6.3	8.5
		SB 207499	472	6.25	2.25	2.5	29.0	468	0.16	1.95	-10.5	13.8

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Gamma Glutamyl Transferase (IU/L)	BASELINE	PLACEBO	243	39.37	34.66	9.0	324.0	0	.	.	.	.
		SB 207499	476	40.63	35.54	9.0	368.0	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	231	38.15	27.86	9.0	204.0	231	-0.96	17.94	-136.0	67.0
		SB 207499	470	40.97	41.02	7.0	443.0	466	-0.03	21.92	-139.0	209.0
	VISIT 2/WEEK 1	PLACEBO	229	41.46	63.08	8.0	892.0	229	1.30	58.24	-138.0	838.0
		SB 207499	448	40.34	39.96	7.0	487.0	444	-1.11	19.41	-144.0	144.0
	VISIT 3/WEEK 2	PLACEBO	221	40.41	53.14	9.0	718.0	221	-0.23	48.51	-139.0	664.0
		SB 207499	447	41.51	49.73	7.0	663.0	445	0.94	38.20	-146.0	643.0
	VISIT 4/WEEK 4	PLACEBO	210	37.59	28.57	9.0	210.0	210	-1.34	22.19	-133.0	188.0
		SB 207499	440	41.76	41.60	8.0	381.0	437	0.17	24.75	-140.0	261.0
	VISIT 5/WEEK 8	PLACEBO	208	38.70	34.27	10.0	351.0	208	-1.39	23.08	-166.0	172.0
		SB 207499	433	39.63	37.89	5.0	408.0	431	-1.29	18.12	-138.0	111.0
	VISIT 6/WEEK 12	PLACEBO	202	36.39	25.11	9.0	161.0	202	-3.87	24.51	-213.0	80.0
		SB 207499	432	42.80	54.47	8.0	806.0	429	1.81	34.44	-142.0	438.0
	VISIT 7/WEEK 16	PLACEBO	193	36.80	26.43	11.0	158.0	193	-2.11	21.14	-166.0	98.0
		SB 207499	424	40.32	45.26	7.0	650.0	421	-0.48	24.92	-134.0	282.0
	VISIT 8/WEEK 20	PLACEBO	192	37.48	31.45	9.0	219.0	192	-1.81	23.63	-153.0	197.0
		SB 207499	428	40.51	43.26	2.0	551.0	425	-1.23	22.05	-125.0	183.0
	VISIT 9/WEEK 24	PLACEBO	189	36.90	28.99	9.0	220.0	189	-3.17	17.88	-104.0	54.0
		SB 207499	417	41.29	44.62	8.0	487.0	414	-0.41	23.34	-143.0	196.0
	VISIT 10/WEEK 28	PLACEBO	184	36.48	30.79	9.0	268.0	184	-3.53	20.62	-134.0	99.0
		SB 207499	411	41.38	46.49	7.0	526.0	408	-0.49	24.34	-133.0	194.0
	VISIT 11/WEEK 32	PLACEBO	186	35.63	28.11	9.0	195.0	186	-4.03	21.86	-134.0	113.0
		SB 207499	410	41.46	50.17	7.0	657.0	407	-0.88	26.35	-149.0	289.0
	VISIT 12/WEEK 36	PLACEBO	184	36.09	30.40	9.0	239.0	184	-3.79	18.38	-93.0	58.0
		SB 207499	404	41.15	43.56	8.0	508.0	401	-1.41	22.87	-158.0	140.0
	VISIT 13/WEEK 40	PLACEBO	178	35.46	26.98	10.0	196.0	178	-3.90	18.98	-128.0	63.0
		SB 207499	393	43.05	54.87	6.0	556.0	390	0.81	34.61	-91.0	381.0
	VISIT 14/WEEK 44	PLACEBO	180	36.94	31.88	7.0	297.0	180	-2.78	22.57	-141.0	118.0
		SB 207499	395	43.64	54.18	7.0	657.0	392	0.80	31.73	-134.0	289.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Gamma Glutamyl Transferase (IU/L)	VISIT 15/WEEK 48	PLACEBO	180	36.17	26.26	9.0	178.0	180	-3.05	23.86	-214.0	81.0
		SB 207499	385	41.72	47.19	8.0	522.0	382	-1.13	24.10	-154.0	171.0
	VISIT 16/WEEK 52	PLACEBO	177	37.71	31.44	11.0	288.0	177	-2.44	26.56	-220.0	109.0
		SB 207499	372	41.11	44.73	8.0	433.0	369	-0.62	24.99	-148.0	178.0
	VISIT 17/WEEK 56	PLACEBO	165	39.47	40.22	11.0	431.0	165	-0.95	31.87	-166.0	252.0
		SB 207499	355	43.28	58.08	9.0	809.0	352	1.96	48.44	-123.0	782.0
	VISIT 18/WEEK 60	PLACEBO	169	37.30	29.20	11.0	200.0	169	-1.58	24.42	-151.0	126.0
		SB 207499	362	41.86	44.49	9.0	453.0	359	-0.02	27.29	-147.0	165.0
	VISIT 19/WEEK 64	PLACEBO	138	37.00	26.42	4.0	139.0	138	-0.39	20.15	-101.0	69.0
		SB 207499	296	40.24	39.98	9.0	316.0	293	0.08	27.71	-141.0	199.0
	VISIT 20/WEEK 68	PLACEBO	135	35.60	24.04	9.0	161.0	135	-1.90	18.98	-79.0	55.0
		SB 207499	292	40.30	42.29	9.0	443.0	289	-0.31	25.50	-129.0	170.0
	VISIT 21/WEEK 72	PLACEBO	170	40.36	38.88	9.0	342.0	170	0.15	34.28	-185.0	251.0
		SB 207499	352	43.29	50.96	8.0	651.0	349	0.54	28.85	-127.0	283.0
	VISIT 22/WEEK 76	PLACEBO	97	36.94	30.05	9.0	224.0	97	-0.48	27.29	-73.0	191.0
		SB 207499	196	40.68	39.12	7.0	265.0	194	1.35	26.31	-72.0	173.0
	VISIT 23/WEEK 80	PLACEBO	98	36.49	33.52	8.0	306.0	98	-1.01	25.33	-58.0	180.0
		SB 207499	187	40.54	39.94	10.0	302.0	186	0.11	26.72	-98.0	167.0
	VISIT 24/WEEK 84	PLACEBO	159	40.17	39.44	10.0	389.0	159	-0.61	27.72	-125.0	210.0
		SB 207499	331	42.80	45.20	8.0	393.0	329	0.47	30.52	-102.0	297.0
	VISIT 25/WEEK 88	PLACEBO	52	33.13	20.43	10.0	98.0	52	-2.40	15.93	-51.0	39.0
		SB 207499	97	38.26	37.92	12.0	273.0	96	0.20	34.31	-127.0	197.0
	VISIT 26/WEEK 92	PLACEBO	52	32.58	18.05	9.0	83.0	52	-3.25	16.67	-52.0	45.0
		SB 207499	93	39.15	43.80	12.0	325.0	92	1.26	40.03	-145.0	249.0
	VISIT 27/WEEK 96	PLACEBO	159	39.43	37.16	10.0	317.0	159	-1.40	23.77	-112.0	138.0
		SB 207499	323	44.33	58.78	8.0	619.0	321	3.22	45.83	-142.0	600.0
	VISIT 28/WEEK 10	PLACEBO	21	32.05	26.00	10.0	123.0	21	3.81	20.47	-38.0	74.0
		SB 207499	49	47.18	57.18	10.0	278.0	49	8.63	49.03	-72.0	187.0
	VISIT 29/WEEK 10	PLACEBO	18	32.94	19.48	12.0	96.0	18	2.00	14.19	-34.0	38.0
		SB 207499	40	51.23	66.17	12.0	352.0	40	11.40	60.05	-78.0	307.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.14

DESCRIPTIVE STATISTICS FOR CLINICAL LABORATORIES BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Gamma Glutamyl Transferase (IU/L)	VISIT 30/WEEK 10	PLACEBO	130	42.67	39.62	10.0	300.0	130	1.11	30.09	-113.0	171.0
		SB 207499	270	44.95	55.05	9.0	664.0	268	2.62	33.65	-115.0	296.0
	VISIT 31/WEEK 11	PLACEBO	9	34.67	16.44	14.0	70.0	9	3.78	20.88	-40.0	38.0
		SB 207499	18	47.89	39.51	12.0	118.0	18	1.89	28.69	-50.0	67.0
	VISIT 32/WEEK 11	PLACEBO	9	35.11	16.44	13.0	71.0	9	4.22	20.00	-36.0	39.0
		SB 207499	16	48.75	42.02	14.0	143.0	16	1.38	22.96	-49.0	66.0
	VISIT 33/WEEK 12	PLACEBO	88	40.28	28.05	9.0	155.0	88	-1.09	23.73	-91.0	60.0
		SB 207499	182	39.70	37.22	10.0	291.0	181	-1.43	27.94	-128.0	157.0
	VISIT 34/WEEK 12	PLACEBO	3	43.67	26.10	23.0	73.0	3	16.33	12.74	8.0	31.0
		SB 207499	3	96.67	105.88	23.0	218.0	3	24.67	40.20	-1.0	71.0
	VISIT 35/WEEK 12	PLACEBO	3	40.33	25.15	22.0	69.0	3	13.00	12.49	3.0	27.0
		SB 207499	3	82.33	78.24	23.0	171.0	3	10.33	12.66	-1.0	24.0
	VISIT 36/WEEK 13	PLACEBO	31	39.61	24.79	14.0	97.0	31	4.71	21.37	-59.0	65.0
		SB 207499	58	41.38	43.61	12.0	232.0	57	-2.28	26.14	-63.0	121.0
	VISIT 37/WEEK 13	PLACEBO	1	36.00	.	36.0	36.0	1	-6.00	.	-6.0	-6.0
		SB 207499	2	67.50	64.35	22.0	113.0	2	-18.00	22.63	-34.0	-2.0
ENDPOINT		PLACEBO	238	41.73	55.41	9.0	718.0	238	2.29	50.02	-119.0	664.0
		SB 207499	472	44.69	54.81	7.0	664.0	468	3.53	36.93	-128.0	297.0

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: HEMOGLOBIN TIME POINT: TOTAL ON-THERAPY

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----						HIGH	HIGH CONCERN
			LOW CONCERN		LOW		NORMAL			
PLACEBO	LOW CONCERN (<0.8xLLN)	1	0		0		1	(100.0%)	0	0
	LOW (0.8xLLN -<1xLLN)	13	2	(15.4%)	8	(61.5%)	3	(23.1%)	0	0
	NORMAL (1xLLN-1xULN)	214	2	(0.9%)	26	(12.1%)	160	(74.8%)	29	(13.6%)
	HIGH (>1xULN-1.2xULN)	10	0		0		1	(10.0%)	9	(90.0%)
	HIGH CONCERN (>1.2xULN)	1	0		0		1	(100.0%)	0	0
	MISSING	0	0		0		0		0	0
	TOTAL	239	4	(1.7%)	34	(14.2%)	166	(69.5%)	38	(15.9%)
SB 207499	LOW CONCERN (<0.8xLLN)	0	0		0		0		0	0
	LOW (0.8xLLN -<1xLLN)	21	1	(4.8%)	15	(71.4%)	5	(23.8%)	0	0
	NORMAL (1xLLN-1xULN)	418	3	(0.7%)	59	(14.1%)	300	(71.8%)	56	(13.4%)
	HIGH (>1xULN-1.2xULN)	31	0		0		2	(6.5%)	29	(93.5%)
	HIGH CONCERN (>1.2xULN)	0	0		0		0		0	0
	MISSING	2	0		0		2	(100.0%)	0	0
	TOTAL	472	4	(0.8%)	74	(15.7%)	309	(65.5%)	85	(18.0%)
TOTAL	LOW CONCERN (<0.8xLLN)	1	0		0		1	(100.0%)	0	0
	LOW (0.8xLLN -<1xLLN)	34	3	(8.8%)	23	(67.6%)	8	(23.5%)	0	0
	NORMAL (1xLLN-1xULN)	632	5	(0.8%)	85	(13.4%)	460	(72.8%)	85	(13.4%)
	HIGH (>1xULN-1.2xULN)	41	0		0		3	(7.3%)	38	(92.7%)
	HIGH CONCERN (>1.2xULN)	1	0		0		1	(100.0%)	0	0
	MISSING	2	0		0		2	(100.0%)	0	0
	TOTAL	711	8	(1.1%)	108	(15.2%)	475	(66.8%)	123	(17.3%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

		PARAMETER: HEMOGLOBIN		TIME POINT: ENDPOINT							
PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	LOW CONCERN	LOW	ON-THERAPY	NORMAL	HIGH	HIGH CONCERN			

PLACEBO	LOW CONCERN (<0.8xLLN)	1	0	0	1	(100.0%)	0	0			
	LOW (0.8xLLN -<1xLLN)	13	0	6 (46.2%)	7	(53.8%)	0	0			
	NORMAL (1xLLN-1xULN)	214	2 (0.9%)	6 (2.8%)	197	(92.1%)	9 (4.2%)	0			
	HIGH (>1xULN-1.2xULN)	10	0	0	7	(70.0%)	3 (30.0%)	0			
	HIGH CONCERN (>1.2xULN)	1	0	0	1	(100.0%)	0	0			
	MISSING	0	0	0	0		0	0			
	TOTAL	239	2 (0.8%)	12 (5.0%)	213	(89.1%)	12 (5.0%)	0			
SB 207499	LOW CONCERN (<0.8xLLN)	0	0	0	0		0	0			
	LOW (0.8xLLN -<1xLLN)	21	0	5 (23.8%)	16	(76.2%)	0	0			
	NORMAL (1xLLN-1xULN)	418	1 (0.2%)	17 (4.1%)	382	(91.4%)	17 (4.1%)	1 (0.2%)			
	HIGH (>1xULN-1.2xULN)	31	0	0	15	(48.4%)	16 (51.6%)	0			
	HIGH CONCERN (>1.2xULN)	0	0	0	0		0	0			
	MISSING	2	0	0	2	(100.0%)	0	0			
	TOTAL	472	1 (0.2%)	22 (4.7%)	415	(87.9%)	33 (7.0%)	1 (0.2%)			
TOTAL	LOW CONCERN (<0.8xLLN)	1	0	0	1	(100.0%)	0	0			
	LOW (0.8xLLN -<1xLLN)	34	0	11 (32.4%)	23	(67.6%)	0	0			
	NORMAL (1xLLN-1xULN)	632	3 (0.5%)	23 (3.6%)	579	(91.6%)	26 (4.1%)	1 (0.2%)			
	HIGH (>1xULN-1.2xULN)	41	0	0	22	(53.7%)	19 (46.3%)	0			
	HIGH CONCERN (>1.2xULN)	1	0	0	1	(100.0%)	0	0			
	MISSING	2	0	0	2	(100.0%)	0	0			
	TOTAL	711	3 (0.4%)	34 (4.8%)	628	(88.3%)	45 (6.3%)	1 (0.1%)			

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: HEMATOCRIT TIME POINT: TOTAL ON-THERAPY

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----						HIGH	HIGH CONCERN
			LOW CONCERN		LOW		NORMAL			
PLACEBO	LOW CONCERN (<0.8xLLN)	1	0		0		1	(100.0%)	0	0
	LOW (0.8xLLN -<1xLLN)	10	4	(40.0%)	5	(50.0%)	0		1	(10.0%)
	NORMAL (1xLLN-1xULN)	200	1	(0.5%)	25	(12.5%)	118	(59.0%)	60	(30.0%)
	HIGH (>1xULN-1.2xULN)	27	0		1	(3.7%)	1	(3.7%)	26	(96.3%)
	HIGH CONCERN (>1.2xULN)	1	0		0		1	(100.0%)	0	
	MISSING	0	0		0		0		0	
	TOTAL	239	5	(2.1%)	31	(13.0%)	121	(50.6%)	87	(36.4%)
SB 207499	LOW CONCERN (<0.8xLLN)	0	0		0		0		0	
	LOW (0.8xLLN -<1xLLN)	19	1	(5.3%)	16	(84.2%)	2	(10.5%)	0	
	NORMAL (1xLLN-1xULN)	405	1	(0.2%)	64	(15.8%)	219	(54.1%)	125	(30.9%)
	HIGH (>1xULN-1.2xULN)	46	0		1	(2.2%)	6	(13.0%)	37	(80.4%)
	HIGH CONCERN (>1.2xULN)	0	0		0		0		0	
	MISSING	2	0		0		1	(50.0%)	1	(50.0%)
	TOTAL	472	2	(0.4%)	81	(17.2%)	228	(48.3%)	163	(34.5%)
TOTAL	LOW CONCERN (<0.8xLLN)	1	0		0		1	(100.0%)	0	
	LOW (0.8xLLN -<1xLLN)	29	5	(17.2%)	21	(72.4%)	2	(6.9%)	1	(3.4%)
	NORMAL (1xLLN-1xULN)	605	2	(0.3%)	89	(14.7%)	337	(55.7%)	185	(30.6%)
	HIGH (>1xULN-1.2xULN)	73	0		2	(2.7%)	7	(9.6%)	63	(86.3%)
	HIGH CONCERN (>1.2xULN)	1	0		0		1	(100.0%)	0	
	MISSING	2	0		0		1	(50.0%)	1	(50.0%)
	TOTAL	711	7	(1.0%)	112	(15.8%)	349	(49.1%)	250	(35.2%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

		PARAMETER: HEMATOCRIT		TIME POINT: ENDPOINT							
PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	LOW CONCERN		LOW		-ON-THERAPY- NORMAL		HIGH	HIGH CONCERN	

PLACEBO	LOW CONCERN (<0.8xLLN)	1	0		0		1	(100.0%)	0		0
	LOW (0.8xLLN -<1xLLN)	10	1	(10.0%)	5	(50.0%)	4	(40.0%)	0		0
	NORMAL (1xLLN-1xULN)	200	1	(0.5%)	9	(4.5%)	176	(88.0%)	14	(7.0%)	0
	HIGH (>1xULN-1.2xULN)	27	0		0		10	(37.0%)	17	(63.0%)	0
	HIGH CONCERN (>1.2xULN)	1	0		0		1	(100.0%)	0		0
	MISSING	0	0		0		0		0		0
	TOTAL	239	2	(0.8%)	14	(5.9%)	192	(80.3%)	31	(13.0%)	0
SB 207499	LOW CONCERN (<0.8xLLN)	0	0		0		0		0		0
	LOW (0.8xLLN -<1xLLN)	19	0		7	(36.8%)	12	(63.2%)	0		0
	NORMAL (1xLLN-1xULN)	405	0		18	(4.4%)	353	(87.2%)	34	(8.4%)	0
	HIGH (>1xULN-1.2xULN)	46	0		1	(2.2%)	19	(41.3%)	25	(54.3%)	1 (2.2%)
	HIGH CONCERN (>1.2xULN)	0	0		0		0		0		0
	MISSING	2	0		0		2	(100.0%)	0		0
	TOTAL	472	0		26	(5.5%)	386	(81.8%)	59	(12.5%)	1 (0.2%)
TOTAL	LOW CONCERN (<0.8xLLN)	1	0		0		1	(100.0%)	0		0
	LOW (0.8xLLN -<1xLLN)	29	1	(3.4%)	12	(41.4%)	16	(55.2%)	0		0
	NORMAL (1xLLN-1xULN)	605	1	(0.2%)	27	(4.5%)	529	(87.4%)	48	(7.9%)	0
	HIGH (>1xULN-1.2xULN)	73	0		1	(1.4%)	29	(39.7%)	42	(57.5%)	1 (1.4%)
	HIGH CONCERN (>1.2xULN)	1	0		0		1	(100.0%)	0		0
	MISSING	2	0		0		2	(100.0%)	0		0
	TOTAL	711	2	(0.3%)	40	(5.6%)	578	(81.3%)	90	(12.7%)	1 (0.1%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: RED BLOOD CELL COUNT		TIME POINT: TOTAL ON-THERAPY						
PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			LOW		NORMAL		HIGH	

PLACEBO	LOW (<1xLLN)	17	13	(76.5%)	4	(23.5%)	0	
	NORMAL (1xLLN-1xULN)	215	32	(14.9%)	171	(79.5%)	14	(6.5%)
	HIGH (>1xULN)	7	0		3	(42.9%)	4	(57.1%)
	MISSING	0	0		0		0	
	TOTAL	239	45	(18.8%)	178	(74.5%)	18	(7.5%)
SB 207499	LOW (<1xLLN)	25	20	(80.0%)	5	(20.0%)	0	
	NORMAL (1xLLN-1xULN)	430	64	(14.9%)	334	(77.7%)	32	(7.4%)
	HIGH (>1xULN)	15	0		2	(13.3%)	13	(86.7%)
	MISSING	2	0		2	(100.0%)	0	
	TOTAL	472	84	(17.8%)	343	(72.7%)	45	(9.5%)
TOTAL	LOW (<1xLLN)	42	33	(78.6%)	9	(21.4%)	0	
	NORMAL (1xLLN-1xULN)	645	96	(14.9%)	505	(78.3%)	46	(7.1%)
	HIGH (>1xULN)	22	0		5	(22.7%)	17	(77.3%)
	MISSING	2	0		2	(100.0%)	0	
	TOTAL	711	129	(18.1%)	521	(73.3%)	63	(8.9%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: RED BLOOD CELL COUNT TIME POINT: ENDPOINT

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			LOW		NORMAL		HIGH	

PLACEBO	LOW (<1xLLN)	17	7	(41.2%)	10	(58.8%)	0	
	NORMAL (1xLLN-1xULN)	215	6	(2.8%)	207	(96.3%)	2	(0.9%)
	HIGH (>1xULN)	7	0		5	(71.4%)	2	(28.6%)
	MISSING	0	0		0		0	
	TOTAL	239	13	(5.4%)	222	(92.9%)	4	(1.7%)
SB 207499	LOW (<1xLLN)	25	16	(64.0%)	9	(36.0%)	0	
	NORMAL (1xLLN-1xULN)	430	15	(3.5%)	409	(95.1%)	6	(1.4%)
	HIGH (>1xULN)	15	0		8	(53.3%)	7	(46.7%)
	MISSING	2	0		2	(100.0%)	0	
	TOTAL	472	31	(6.6%)	428	(90.7%)	13	(2.8%)
TOTAL	LOW (<1xLLN)	42	23	(54.8%)	19	(45.2%)	0	
	NORMAL (1xLLN-1xULN)	645	21	(3.3%)	616	(95.5%)	8	(1.2%)
	HIGH (>1xULN)	22	0		13	(59.1%)	9	(40.9%)
	MISSING	2	0		2	(100.0%)	0	
	TOTAL	711	44	(6.2%)	650	(91.4%)	17	(2.4%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: WHITE BLOOD CELL COUNT TIME POINT: TOTAL ON-THERAPY

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----									
			LOW CONCERN		LOW		NORMAL		HIGH		HIGH CONCERN	
PLACEBO	LOW CONCERN (<=3000/mm3)	0	0		0		0		0		0	
	LOW (>3000/mm3-<1xLLN)	1	0		1	(100.0%)	0		0		0	
	NORMAL (1xLLN-1xULN)	220	3	(1.4%)	7	(3.2%)	148	(67.3%)	62	(28.2%)	2	(0.9%)
	HIGH (>1xULN-<20000/mm3)	18	0		0		3	(16.7%)	13	(72.2%)	2	(11.1%)
	HIGH CONCERN (>=20000/mm3)	0	0		0		0		0		0	
	MISSING	0	0		0		0		0		0	
	TOTAL	239	3	(1.3%)	8	(3.3%)	151	(63.2%)	75	(31.4%)	4	(1.7%)
SB 207499	LOW CONCERN (<=3000/mm3)	0	0		0		0		0		0	
	LOW (>3000/mm3-<1xLLN)	2	0		1	(50.0%)	1	(50.0%)	0		0	
	NORMAL (1xLLN-1xULN)	442	3	(0.7%)	14	(3.2%)	269	(60.9%)	153	(34.6%)	4	(0.9%)
	HIGH (>1xULN-<20000/mm3)	26	0		0		3	(11.5%)	21	(80.8%)	2	(7.7%)
	HIGH CONCERN (>=20000/mm3)	0	0		0		0		0		0	
	MISSING	2	0		0		1	(50.0%)	1	(50.0%)	0	
	TOTAL	472	3	(0.6%)	15	(3.2%)	274	(58.1%)	175	(37.1%)	6	(1.3%)
TOTAL	LOW CONCERN (<=3000/mm3)	0	0		0		0		0		0	
	LOW (>3000/mm3-<1xLLN)	3	0		2	(66.7%)	1	(33.3%)	0		0	
	NORMAL (1xLLN-1xULN)	662	6	(0.9%)	21	(3.2%)	417	(63.0%)	215	(32.5%)	6	(0.9%)
	HIGH (>1xULN-<20000/mm3)	44	0		0		6	(13.6%)	34	(77.3%)	4	(9.1%)
	HIGH CONCERN (>=20000/mm3)	0	0		0		0		0		0	
	MISSING	2	0		0		1	(50.0%)	1	(50.0%)	0	
	TOTAL	711	6	(0.8%)	23	(3.2%)	425	(59.8%)	250	(35.2%)	10	(1.4%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: WHITE BLOOD CELL COUNT TIME POINT: ENDPOINT

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN	
PLACEBO	LOW CONCERN ($\leq 3000/\text{mm}^3$)	0	0	0	0	0	0	
	LOW ($>3000/\text{mm}^3 - < 1 \times \text{LLN}$)	1	0	0	1 (100.0%)	0	0	
	NORMAL ($1 \times \text{LLN} - 1 \times \text{ULN}$)	220	0	1 (0.5%)	209 (95.0%)	9 (4.1%)	1 (0.5%)	
	HIGH ($> 1 \times \text{ULN} - < 20000/\text{mm}^3$)	18	0	0	13 (72.2%)	4 (22.2%)	1 (5.6%)	
	HIGH CONCERN ($\geq 20000/\text{mm}^3$)	0	0	0	0	0	0	
	MISSING	0	0	0	0	0	0	
	TOTAL	239	0	1 (0.4%)	223 (93.3%)	13 (5.4%)	2 (0.8%)	
SB 207499	LOW CONCERN ($\leq 3000/\text{mm}^3$)	0	0	0	0	0	0	
	LOW ($>3000/\text{mm}^3 - < 1 \times \text{LLN}$)	2	0	0	2 (100.0%)	0	0	
	NORMAL ($1 \times \text{LLN} - 1 \times \text{ULN}$)	442	0	3 (0.7%)	415 (93.9%)	23 (5.2%)	1 (0.2%)	
	HIGH ($> 1 \times \text{ULN} - < 20000/\text{mm}^3$)	26	0	0	18 (69.2%)	8 (30.8%)	0	
	HIGH CONCERN ($\geq 20000/\text{mm}^3$)	0	0	0	0	0	0	
	MISSING	2	0	0	2 (100.0%)	0	0	
	TOTAL	472	0	3 (0.6%)	437 (92.6%)	31 (6.6%)	1 (0.2%)	
TOTAL	LOW CONCERN ($\leq 3000/\text{mm}^3$)	0	0	0	0	0	0	
	LOW ($>3000/\text{mm}^3 - < 1 \times \text{LLN}$)	3	0	0	3 (100.0%)	0	0	
	NORMAL ($1 \times \text{LLN} - 1 \times \text{ULN}$)	662	0	4 (0.6%)	624 (94.3%)	32 (4.8%)	2 (0.3%)	
	HIGH ($> 1 \times \text{ULN} - < 20000/\text{mm}^3$)	44	0	0	31 (70.5%)	12 (27.3%)	1 (2.3%)	
	HIGH CONCERN ($\geq 20000/\text{mm}^3$)	0	0	0	0	0	0	
	MISSING	2	0	0	2 (100.0%)	0	0	
	TOTAL	711	0	4 (0.6%)	660 (92.8%)	44 (6.2%)	3 (0.4%)	

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PLATELETS TIME POINT: TOTAL ON-THERAPY

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----						HIGH	HIGH CONCERN
			LOW CONCERN		LOW		NORMAL			
PLACEBO	LOW CONCERN (<100 BILLION/L)	0	0		0		0		0	
	LOW (100 BILLION/L-<1xLLN)	7	3 (42.9%)		2 (28.6%)		2 (28.6%)		0	
	NORMAL (1xLLN-1xULN)	229	5 (2.2%)		14 (6.1%)		186 (81.2%)		15 (6.6%)	10 (4.4%)
	HIGH (>1xULN-500 BILLION/L)	3	0		0		1 (33.3%)		1 (33.3%)	1 (33.3%)
	HIGH CONCERN (>500 BILLION/L)	0	0		0		0		0	
	MISSING	0	0		0		0		0	
	TOTAL	239	8 (3.3%)		16 (6.7%)		189 (79.1%)		16 (6.7%)	11 (4.6%)
SB 207499	LOW CONCERN (<100 BILLION/L)	1	0		1 (100.0%)		0		0	
	LOW (100 BILLION/L-<1xLLN)	5	2 (40.0%)		2 (40.0%)		1 (20.0%)		0	
	NORMAL (1xLLN-1xULN)	448	10 (2.2%)		21 (4.7%)		356 (79.5%)		50 (11.2%)	14 (3.1%)
	HIGH (>1xULN-500 BILLION/L)	11	0		0		2 (18.2%)		3 (27.3%)	6 (54.5%)
	HIGH CONCERN (>500 BILLION/L)	5	0		0		0		1 (20.0%)	4 (80.0%)
	MISSING	2	0		0		2 (100.0%)		0	
	TOTAL	472	12 (2.5%)		24 (5.1%)		361 (76.5%)		54 (11.4%)	24 (5.1%)
TOTAL	LOW CONCERN (<100 BILLION/L)	1	0		1 (100.0%)		0		0	
	LOW (100 BILLION/L-<1xLLN)	12	5 (41.7%)		4 (33.3%)		3 (25.0%)		0	
	NORMAL (1xLLN-1xULN)	677	15 (2.2%)		35 (5.2%)		542 (80.1%)		65 (9.6%)	24 (3.5%)
	HIGH (>1xULN-500 BILLION/L)	14	0		0		3 (21.4%)		4 (28.6%)	7 (50.0%)
	HIGH CONCERN (>500 BILLION/L)	5	0		0		0		1 (20.0%)	4 (80.0%)
	MISSING	2	0		0		2 (100.0%)		0	
	TOTAL	711	20 (2.8%)		40 (5.6%)		550 (77.4%)		70 (9.8%)	35 (4.9%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

		PARAMETER: PLATELETS		TIME POINT: ENDPOINT								
PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	LOW CONCERN		LOW		-ON-THERAPY- NORMAL		HIGH		HIGH CONCERN	

PLACEBO	LOW CONCERN (<100 BILLION/L)	0	0		0		0		0		0	
	LOW (100 BILLION/L-<1xLLN)	7	2	(28.6%)	3	(42.9%)	2	(28.6%)	0		0	
	NORMAL (1xLLN-1xULN)	229	0		2	(0.9%)	221	(96.5%)	5	(2.2%)	1	(0.4%)
	HIGH (>1xULN-500 BILLION/L)	3	0		0		2	(66.7%)	0		1	(33.3%)
	HIGH CONCERN (>500 BILLION/L)	0	0		0		0		0		0	
	MISSING	0	0		0		0		0		0	
	TOTAL	239	2	(0.8%)	5	(2.1%)	225	(94.1%)	5	(2.1%)	2	(0.8%)
SB 207499	LOW CONCERN (<100 BILLION/L)	1	0		0		1	(100.0%)	0		0	
	LOW (100 BILLION/L-<1xLLN)	5	0		1	(20.0%)	4	(80.0%)	0		0	
	NORMAL (1xLLN-1xULN)	448	0		5	(1.1%)	424	(94.6%)	15	(3.3%)	4	(0.9%)
	HIGH (>1xULN-500 BILLION/L)	11	0		0		5	(45.5%)	5	(45.5%)	1	(9.1%)
	HIGH CONCERN (>500 BILLION/L)	5	0		0		1	(20.0%)	3	(60.0%)	1	(20.0%)
	MISSING	2	0		0		2	(100.0%)	0		0	
	TOTAL	472	0		6	(1.3%)	437	(92.6%)	23	(4.9%)	6	(1.3%)
TOTAL	LOW CONCERN (<100 BILLION/L)	1	0		0		1	(100.0%)	0		0	
	LOW (100 BILLION/L-<1xLLN)	12	2	(16.7%)	4	(33.3%)	6	(50.0%)	0		0	
	NORMAL (1xLLN-1xULN)	677	0		7	(1.0%)	645	(95.3%)	20	(3.0%)	5	(0.7%)
	HIGH (>1xULN-500 BILLION/L)	14	0		0		7	(50.0%)	5	(35.7%)	2	(14.3%)
	HIGH CONCERN (>500 BILLION/L)	5	0		0		1	(20.0%)	3	(60.0%)	1	(20.0%)
	MISSING	2	0		0		2	(100.0%)	0		0	
	TOTAL	711	2	(0.3%)	11	(1.5%)	662	(93.1%)	28	(3.9%)	8	(1.1%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: BASOPHILS ABSOLUTE		TIME POINT: TOTAL ON-THERAPY				
PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	LOW	ON-THERAPY		HIGH
				NORMAL		
PLACEBO	LOW (<1xLLN)	0	0	0		0
	NORMAL (1xLLN-1xULN)	239	0	238 (99.6%)		1 (0.4%)
	HIGH (>1xULN)	0	0	0		0
	MISSING	0	0	0		0
	TOTAL	239	0	238 (99.6%)		1 (0.4%)
SB 207499	LOW (<1xLLN)	0	0	0		0
	NORMAL (1xLLN-1xULN)	470	0	468 (99.6%)		2 (0.4%)
	HIGH (>1xULN)	0	0	0		0
	MISSING	2	0	2 (100.0%)		0
	TOTAL	472	0	470 (99.6%)		2 (0.4%)
TOTAL	LOW (<1xLLN)	0	0	0		0
	NORMAL (1xLLN-1xULN)	709	0	706 (99.6%)		3 (0.4%)
	HIGH (>1xULN)	0	0	0		0
	MISSING	2	0	2 (100.0%)		0
	TOTAL	711	0	708 (99.6%)		3 (0.4%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: BASOPHILS ABSOLUTE TIME POINT: ENDPOINT

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----		
			LOW	NORMAL	HIGH
PLACEBO	LOW (<1xLLN)	0	0	0	0
	NORMAL (1xLLN-1xULN)	239	0	239 (100.0%)	0
	HIGH (>1xULN)	0	0	0	0
	MISSING	0	0	0	0
	TOTAL	239	0	239 (100.0%)	0
SB 207499	LOW (<1xLLN)	0	0	0	0
	NORMAL (1xLLN-1xULN)	470	0	470 (100.0%)	0
	HIGH (>1xULN)	0	0	0	0
	MISSING	2	0	2 (100.0%)	0
	TOTAL	472	0	472 (100.0%)	0
TOTAL	LOW (<1xLLN)	0	0	0	0
	NORMAL (1xLLN-1xULN)	709	0	709 (100.0%)	0
	HIGH (>1xULN)	0	0	0	0
	MISSING	2	0	2 (100.0%)	0
	TOTAL	711	0	711 (100.0%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: EOSINOPHILS ABSOLUTE		TIME POINT: TOTAL ON-THERAPY					
PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	NORMAL		ON-THERAPY HIGH		CONCERN
PLACEBO	NORMAL ($\leq 1 \times \text{ULN}$)	224	188	(83.9%)	34	(15.2%)	2 (0.9%)
	HIGH ($> 1 \times \text{ULN} - 2 \times \text{ULN}$)	13	5	(38.5%)	8	(61.5%)	0
	CONCERN ($> 2 \times \text{ULN}$)	2	0		0		2 (100.0%)
	MISSING	0	0		0		0
	TOTAL	239	193	(80.8%)	42	(17.6%)	4 (1.7%)
SB 207499	NORMAL ($\leq 1 \times \text{ULN}$)	455	388	(85.3%)	61	(13.4%)	6 (1.3%)
	HIGH ($> 1 \times \text{ULN} - 2 \times \text{ULN}$)	15	1	(6.7%)	13	(86.7%)	1 (6.7%)
	CONCERN ($> 2 \times \text{ULN}$)	0	0		0		0
	MISSING	2	1	(50.0%)	1	(50.0%)	0
	TOTAL	472	390	(82.6%)	75	(15.9%)	7 (1.5%)
TOTAL	NORMAL ($\leq 1 \times \text{ULN}$)	679	576	(84.8%)	95	(14.0%)	8 (1.2%)
	HIGH ($> 1 \times \text{ULN} - 2 \times \text{ULN}$)	28	6	(21.4%)	21	(75.0%)	1 (3.6%)
	CONCERN ($> 2 \times \text{ULN}$)	2	0		0		2 (100.0%)
	MISSING	2	1	(50.0%)	1	(50.0%)	0
	TOTAL	711	583	(82.0%)	117	(16.5%)	11 (1.5%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: EOSINOPHILS ABSOLUTE TIME POINT: ENDPOINT

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL ($\leq 1 \times \text{ULN}$)	224	215	(96.0%)	9	(4.0%)	0
	HIGH ($> 1 \times \text{ULN} - 2 \times \text{ULN}$)	13	10	(76.9%)	3	(23.1%)	0
	CONCERN ($> 2 \times \text{ULN}$)	2	0		1	(50.0%)	1 (50.0%)
	MISSING	0	0		0		0
	TOTAL	239	225	(94.1%)	13	(5.4%)	1 (0.4%)
SB 207499	NORMAL ($\leq 1 \times \text{ULN}$)	455	444	(97.6%)	11	(2.4%)	0
	HIGH ($> 1 \times \text{ULN} - 2 \times \text{ULN}$)	15	12	(80.0%)	3	(20.0%)	0
	CONCERN ($> 2 \times \text{ULN}$)	0	0		0		0
	MISSING	2	2	(100.0%)	0		0
	TOTAL	472	458	(97.0%)	14	(3.0%)	0
TOTAL	NORMAL ($\leq 1 \times \text{ULN}$)	679	659	(97.1%)	20	(2.9%)	0
	HIGH ($> 1 \times \text{ULN} - 2 \times \text{ULN}$)	28	22	(78.6%)	6	(21.4%)	0
	CONCERN ($> 2 \times \text{ULN}$)	2	0		1	(50.0%)	1 (50.0%)
	MISSING	2	2	(100.0%)	0		0
	TOTAL	711	683	(96.1%)	27	(3.8%)	1 (0.1%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: LYMPHOCYTES ABSOLUTE		TIME POINT: TOTAL ON-THERAPY							
PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----						
			LOW		NORMAL		HIGH		

PLACEBO	LOW (<1xLLN)	4	3	(75.0%)	1	(25.0%)	0		
	NORMAL (1xLLN-1xULN)	231	20	(8.7%)	202	(87.4%)	9	(3.9%)	
	HIGH (>1xULN)	4	0		2	(50.0%)	2	(50.0%)	
	MISSING	0	0		0		0		
	TOTAL	239	23	(9.6%)	205	(85.8%)	11	(4.6%)	
SB 207499	LOW (<1xLLN)	3	2	(66.7%)	1	(33.3%)	0		
	NORMAL (1xLLN-1xULN)	464	42	(9.1%)	390	(84.1%)	33	(7.1%)	
	HIGH (>1xULN)	3	0		0		3	(100.0%)	
	MISSING	2	0		2	(100.0%)	0		
	TOTAL	472	44	(9.3%)	393	(83.3%)	36	(7.6%)	
TOTAL	LOW (<1xLLN)	7	5	(71.4%)	2	(28.6%)	0		
	NORMAL (1xLLN-1xULN)	695	62	(8.9%)	592	(85.2%)	42	(6.0%)	
	HIGH (>1xULN)	7	0		2	(28.6%)	5	(71.4%)	
	MISSING	2	0		2	(100.0%)	0		
	TOTAL	711	67	(9.4%)	598	(84.1%)	47	(6.6%)	

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: LYMPHOCYTES ABSOLUTE TIME POINT: ENDPOINT

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			LOW		NORMAL		HIGH
PLACEBO	LOW (<1xLLN)	4	3	(75.0%)	1	(25.0%)	0
	NORMAL (1xLLN-1xULN)	231	7	(3.0%)	224	(97.0%)	0
	HIGH (>1xULN)	4	0		2	(50.0%)	2 (50.0%)
	MISSING	0	0		0		0
	TOTAL	239	10	(4.2%)	227	(95.0%)	2 (0.8%)
SB 207499	LOW (<1xLLN)	3	1	(33.3%)	2	(66.7%)	0
	NORMAL (1xLLN-1xULN)	464	1	(0.2%)	460	(99.1%)	3 (0.6%)
	HIGH (>1xULN)	3	0		1	(33.3%)	2 (66.7%)
	MISSING	2	0		2	(100.0%)	0
	TOTAL	472	2	(0.4%)	465	(98.5%)	5 (1.1%)
TOTAL	LOW (<1xLLN)	7	4	(57.1%)	3	(42.9%)	0
	NORMAL (1xLLN-1xULN)	695	8	(1.2%)	684	(98.4%)	3 (0.4%)
	HIGH (>1xULN)	7	0		3	(42.9%)	4 (57.1%)
	MISSING	2	0		2	(100.0%)	0
	TOTAL	711	12	(1.7%)	692	(97.3%)	7 (1.0%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: MONOCYTES ABSOLUTE		TIME POINT: TOTAL ON-THERAPY						
PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			LOW		NORMAL		HIGH	

PLACEBO	LOW (<1xLLN)	8	4	(50.0%)	4	(50.0%)	0	
	NORMAL (1xLLN-1xULN)	226	41	(18.1%)	166	(73.5%)	21	(9.3%)
	HIGH (>1xULN)	5	2	(40.0%)	0		3	(60.0%)
	MISSING	0	0		0		0	
	TOTAL	239	47	(19.7%)	170	(71.1%)	24	(10.0%)
SB 207499	LOW (<1xLLN)	12	6	(50.0%)	6	(50.0%)	0	
	NORMAL (1xLLN-1xULN)	450	106	(23.6%)	297	(66.0%)	62	(13.8%)
	HIGH (>1xULN)	8	1	(12.5%)	4	(50.0%)	4	(50.0%)
	MISSING	2	1	(50.0%)	1	(50.0%)	0	
	TOTAL	472	114	(24.2%)	308	(65.3%)	66	(14.0%)
TOTAL	LOW (<1xLLN)	20	10	(50.0%)	10	(50.0%)	0	
	NORMAL (1xLLN-1xULN)	676	147	(21.7%)	463	(68.5%)	83	(12.3%)
	HIGH (>1xULN)	13	3	(23.1%)	4	(30.8%)	7	(53.8%)
	MISSING	2	1	(50.0%)	1	(50.0%)	0	
	TOTAL	711	161	(22.6%)	478	(67.2%)	90	(12.7%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: MONOCYTES ABSOLUTE TIME POINT: ENDPOINT

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			LOW		NORMAL		HIGH	

PLACEBO	LOW (<1xLLN)	8	2	(25.0%)	6	(75.0%)	0	
	NORMAL (1xLLN-1xULN)	226	3	(1.3%)	221	(97.8%)	2	(0.9%)
	HIGH (>1xULN)	5	0		3	(60.0%)	2	(40.0%)
	MISSING	0	0		0		0	
	TOTAL	239	5	(2.1%)	230	(96.2%)	4	(1.7%)
SB 207499	LOW (<1xLLN)	12	2	(16.7%)	10	(83.3%)	0	
	NORMAL (1xLLN-1xULN)	450	14	(3.1%)	433	(96.2%)	3	(0.7%)
	HIGH (>1xULN)	8	0		6	(75.0%)	2	(25.0%)
	MISSING	2	0		2	(100.0%)	0	
	TOTAL	472	16	(3.4%)	451	(95.6%)	5	(1.1%)
TOTAL	LOW (<1xLLN)	20	4	(20.0%)	16	(80.0%)	0	
	NORMAL (1xLLN-1xULN)	676	17	(2.5%)	654	(96.7%)	5	(0.7%)
	HIGH (>1xULN)	13	0		9	(69.2%)	4	(30.8%)
	MISSING	2	0		2	(100.0%)	0	
	TOTAL	711	21	(3.0%)	681	(95.8%)	9	(1.3%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: NEUTROPHILS ABSOLUTE TIME POINT: TOTAL ON-THERAPY

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----						HIGH	HIGH CONCERN
			LOW CONCERN		LOW		NORMAL			
PLACEBO	LOW CONCERN (<0.8xLLN)	0	0		0		0		0	0
	LOW (0.8xLLN-<1xLLN)	1	0		1	(100.0%)	0		0	0
	NORMAL (1xLLN-1xULN)	228	5	(2.2%)	10	(4.4%)	146	(64.0%)	58	(25.4%)
	HIGH (>1xULN-1.5xULN)	9	1	(11.1%)	0		2	(22.2%)	6	(66.7%)
	HIGH CONCERN (>1.5xULN)	1	0		0		0		1	(100.0%)
	MISSING	0	0		0		0		0	0
	TOTAL	239	6	(2.5%)	11	(4.6%)	148	(61.9%)	65	(27.2%)
SB 207499	LOW CONCERN (<0.8xLLN)	2	1	(50.0%)	0		1	(50.0%)	0	0
	LOW (0.8xLLN-<1xLLN)	2	1	(50.0%)	0		1	(50.0%)	1	(50.0%)
	NORMAL (1xLLN-1xULN)	447	13	(2.9%)	17	(3.8%)	269	(60.2%)	125	(28.0%)
	HIGH (>1xULN-1.5xULN)	17	0		0		3	(17.6%)	7	(41.2%)
	HIGH CONCERN (>1.5xULN)	2	0		0		0		1	(50.0%)
	MISSING	2	0		0		1	(50.0%)	0	1
	TOTAL	472	15	(3.2%)	17	(3.6%)	275	(58.3%)	134	(28.4%)
TOTAL	LOW CONCERN (<0.8xLLN)	2	1	(50.0%)	0		1	(50.0%)	0	0
	LOW (0.8xLLN-<1xLLN)	3	1	(33.3%)	1	(33.3%)	1	(33.3%)	1	(33.3%)
	NORMAL (1xLLN-1xULN)	675	18	(2.7%)	27	(4.0%)	415	(61.5%)	183	(27.1%)
	HIGH (>1xULN-1.5xULN)	26	1	(3.8%)	0		5	(19.2%)	13	(50.0%)
	HIGH CONCERN (>1.5xULN)	3	0		0		0		2	(66.7%)
	MISSING	2	0		0		1	(50.0%)	0	1
	TOTAL	711	21	(3.0%)	28	(3.9%)	423	(59.5%)	199	(28.0%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: NEUTROPHILS ABSOLUTE TIME POINT: ENDPOINT

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN			

PLACEBO	LOW CONCERN (<0.8xLLN)	0	0		0	0		0		0
	LOW (0.8xLLN-<1xLLN)	1	0		1 (100.0%)	0		0		0
	NORMAL (1xLLN-1xULN)	228	0		0	218 (95.6%)	9 (3.9%)	1 (0.4%)		
	HIGH (>1xULN-1.5xULN)	9	1 (11.1%)		0	7 (77.8%)	1 (11.1%)	0		
	HIGH CONCERN (>1.5xULN)	1	0		0	1 (100.0%)	0	0		
	MISSING	0	0		0	0	0	0		
	TOTAL	239	1 (0.4%)	1 (0.4%)	226 (94.6%)	10 (4.2%)	1 (0.4%)			
SB 207499	LOW CONCERN (<0.8xLLN)	2	0		0	2 (100.0%)	0		0	
	LOW (0.8xLLN-<1xLLN)	2	0		0	2 (100.0%)	0		0	
	NORMAL (1xLLN-1xULN)	447	2 (0.4%)	1 (0.2%)	422 (94.4%)	20 (4.5%)	2 (0.4%)			
	HIGH (>1xULN-1.5xULN)	17	0		0	9 (52.9%)	6 (35.3%)	2 (11.8%)		
	HIGH CONCERN (>1.5xULN)	2	0		0	2 (100.0%)	0	0		
	MISSING	2	0		0	2 (100.0%)	0	0		
	TOTAL	472	2 (0.4%)	1 (0.2%)	439 (93.0%)	26 (5.5%)	4 (0.8%)			
TOTAL	LOW CONCERN (<0.8xLLN)	2	0		0	2 (100.0%)	0		0	
	LOW (0.8xLLN-<1xLLN)	3	0		1 (33.3%)	2 (66.7%)	0		0	
	NORMAL (1xLLN-1xULN)	675	2 (0.3%)	1 (0.1%)	640 (94.8%)	29 (4.3%)	3 (0.4%)			
	HIGH (>1xULN-1.5xULN)	26	1 (3.8%)		0	16 (61.5%)	7 (26.9%)	2 (7.7%)		
	HIGH CONCERN (>1.5xULN)	3	0		0	3 (100.0%)	0	0		
	MISSING	2	0		0	2 (100.0%)	0	0		
	TOTAL	711	3 (0.4%)	2 (0.3%)	665 (93.5%)	36 (5.1%)	5 (0.7%)			

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

		PARAMETER: SODIUM		TIME POINT: TOTAL ON-THERAPY										
PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	LOW CONCERN		LOW		-ON-THERAPY-		NORMAL		HIGH		HIGH CONCERN	

PLACEBO	LOW CONCERN (<=130 MMOL/L)	1	1	(100.0%)	0		0		0		0		0	
	LOW (>130 MMOL/L-<1xLLN)	6	3	(50.0%)	1	(16.7%)	2	(33.3%)	0		0		0	
	NORMAL (1xLLN-1xULN)	230	6	(2.6%)	24	(10.4%)	150	(65.2%)	42	(18.3%)	9	(3.9%)		
	HIGH (>1xULN-<150 MMOL/L)	2	0		0		0		2	(100.0%)	0		0	
	HIGH CONCERN (>=150 MMOL/L)	0	0		0		0		0		0		0	
	MISSING	0	0		0		0		0		0		0	
	TOTAL	239	10	(4.2%)	25	(10.5%)	152	(63.6%)	44	(18.4%)	9	(3.8%)		
SB 207499	LOW CONCERN (<=130 MMOL/L)	0	0		0		0		0		0		0	
	LOW (>130 MMOL/L-<1xLLN)	10	1	(10.0%)	6	(60.0%)	2	(20.0%)	0		1	(10.0%)		
	NORMAL (1xLLN-1xULN)	455	10	(2.2%)	58	(12.7%)	283	(62.2%)	95	(20.9%)	19	(4.2%)		
	HIGH (>1xULN-<150 MMOL/L)	2	0		0		1	(50.0%)	1	(50.0%)	0		0	
	HIGH CONCERN (>=150 MMOL/L)	1	0		0		1	(100.0%)	0		0		0	
	MISSING	4	0		0		3	(75.0%)	0		1	(25.0%)		
	TOTAL	472	11	(2.3%)	64	(13.6%)	290	(61.4%)	96	(20.3%)	21	(4.4%)		
TOTAL	LOW CONCERN (<=130 MMOL/L)	1	1	(100.0%)	0		0		0		0		0	
	LOW (>130 MMOL/L-<1xLLN)	16	4	(25.0%)	7	(43.8%)	4	(25.0%)	0		1	(6.3%)		
	NORMAL (1xLLN-1xULN)	685	16	(2.3%)	82	(12.0%)	433	(63.2%)	137	(20.0%)	28	(4.1%)		
	HIGH (>1xULN-<150 MMOL/L)	4	0		0		1	(25.0%)	3	(75.0%)	0		0	
	HIGH CONCERN (>=150 MMOL/L)	1	0		0		1	(100.0%)	0		0		0	
	MISSING	4	0		0		3	(75.0%)	0		1	(25.0%)		
	TOTAL	711	21	(3.0%)	89	(12.5%)	442	(62.2%)	140	(19.7%)	30	(4.2%)		

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

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TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: SODIUM TIME POINT: ENDPOINT

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN	
PLACEBO	LOW CONCERN (≤ 130 MMOL/L)	1	0	1 (100.0%)	0	0	0	
	LOW (>130 MMOL/L- $<1 \times \text{LLN}$)	6	2 (33.3%)	0	4 (66.7%)	0	0	
	NORMAL ($1 \times \text{LLN}$ - $1 \times \text{ULN}$)	230	1 (0.4%)	3 (1.3%)	223 (97.0%)	2 (0.9%)	1 (0.4%)	
	HIGH ($>1 \times \text{ULN}$ - <150 MMOL/L)	2	0	0	2 (100.0%)	0	0	
	HIGH CONCERN (≥ 150 MMOL/L)	0	0	0	0	0	0	
	MISSING	0	0	0	0	0	0	
	TOTAL	239	3 (1.3%)	4 (1.7%)	229 (95.8%)	2 (0.8%)	1 (0.4%)	
SB 207499	LOW CONCERN (≤ 130 MMOL/L)	0	0	0	0	0	0	
	LOW (>130 MMOL/L- $<1 \times \text{LLN}$)	10	0	1 (10.0%)	9 (90.0%)	0	0	
	NORMAL ($1 \times \text{LLN}$ - $1 \times \text{ULN}$)	455	0	6 (1.3%)	436 (95.8%)	12 (2.6%)	1 (0.2%)	
	HIGH ($>1 \times \text{ULN}$ - <150 MMOL/L)	2	0	0	2 (100.0%)	0	0	
	HIGH CONCERN (≥ 150 MMOL/L)	1	0	0	1 (100.0%)	0	0	
	MISSING	4	0	0	4 (100.0%)	0	0	
	TOTAL	472	0	7 (1.5%)	452 (95.8%)	12 (2.5%)	1 (0.2%)	
TOTAL	LOW CONCERN (≤ 130 MMOL/L)	1	0	1 (100.0%)	0	0	0	
	LOW (>130 MMOL/L- $<1 \times \text{LLN}$)	16	2 (12.5%)	1 (6.3%)	13 (81.3%)	0	0	
	NORMAL ($1 \times \text{LLN}$ - $1 \times \text{ULN}$)	685	1 (0.1%)	9 (1.3%)	659 (96.2%)	14 (2.0%)	2 (0.3%)	
	HIGH ($>1 \times \text{ULN}$ - <150 MMOL/L)	4	0	0	4 (100.0%)	0	0	
	HIGH CONCERN (≥ 150 MMOL/L)	1	0	0	1 (100.0%)	0	0	
	MISSING	4	0	0	4 (100.0%)	0	0	
	TOTAL	711	3 (0.4%)	11 (1.5%)	681 (95.8%)	14 (2.0%)	2 (0.3%)	

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: POTASSIUM TIME POINT: TOTAL ON-THERAPY

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN	
PLACEBO	LOW CONCERN (≤ 3.0 MMOL/L)	0	0	0	0	0	0	
	LOW (> 3.0 MMOL/L- $< 1 \times \text{LLN}$)	0	0	0	0	0	0	
	NORMAL ($1 \times \text{LLN}$ - $1 \times \text{ULN}$)	231	2 (0.9%)	2 (0.9%)	185 (80.1%)	10 (4.3%)	32 (13.9%)	
	HIGH ($> 1 \times \text{ULN}$ - < 5.5 MMOL/L)	4	0	0	0	1 (25.0%)	3 (75.0%)	
	HIGH CONCERN (≥ 5.5 MMOL/L)	3	0	0	1 (33.3%)	0	2 (66.7%)	
	MISSING	1	0	0	1 (100.0%)	0	0	
	TOTAL	239	2 (0.8%)	2 (0.8%)	187 (78.2%)	11 (4.6%)	37 (15.5%)	
SB 207499	LOW CONCERN (≤ 3.0 MMOL/L)	0	0	0	0	0	0	
	LOW (> 3.0 MMOL/L- $< 1 \times \text{LLN}$)	0	0	0	0	0	0	
	NORMAL ($1 \times \text{LLN}$ - $1 \times \text{ULN}$)	451	1 (0.2%)	15 (3.3%)	342 (75.8%)	30 (6.7%)	63 (14.0%)	
	HIGH ($> 1 \times \text{ULN}$ - < 5.5 MMOL/L)	3	0	0	1 (33.3%)	0	2 (66.7%)	
	HIGH CONCERN (≥ 5.5 MMOL/L)	14	0	0	5 (35.7%)	2 (14.3%)	7 (50.0%)	
	MISSING	4	0	0	1 (25.0%)	0	3 (75.0%)	
	TOTAL	472	1 (0.2%)	15 (3.2%)	349 (73.9%)	32 (6.8%)	75 (15.9%)	
TOTAL	LOW CONCERN (≤ 3.0 MMOL/L)	0	0	0	0	0	0	
	LOW (> 3.0 MMOL/L- $< 1 \times \text{LLN}$)	0	0	0	0	0	0	
	NORMAL ($1 \times \text{LLN}$ - $1 \times \text{ULN}$)	682	3 (0.4%)	17 (2.5%)	527 (77.3%)	40 (5.9%)	95 (13.9%)	
	HIGH ($> 1 \times \text{ULN}$ - < 5.5 MMOL/L)	7	0	0	1 (14.3%)	1 (14.3%)	5 (71.4%)	
	HIGH CONCERN (≥ 5.5 MMOL/L)	17	0	0	6 (35.3%)	2 (11.8%)	9 (52.9%)	
	MISSING	5	0	0	2 (40.0%)	0	3 (60.0%)	
	TOTAL	711	3 (0.4%)	17 (2.4%)	536 (75.4%)	43 (6.0%)	112 (15.8%)	

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

		PARAMETER: POTASSIUM		TIME POINT: ENDPOINT							
PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	LOW CONCERN	LOW	ON-THERAPY	NORMAL	HIGH	HIGH CONCERN			
PLACEBO	LOW CONCERN (≤ 3.0 MMOL/L)	0	0	0	0	0	0	0			
	LOW (> 3.0 MMOL/L- $< 1 \times \text{LLN}$)	0	0	0	0	0	0	0			
	NORMAL ($1 \times \text{LLN}$ - $1 \times \text{ULN}$)	231	1 (0.4%)	1 (0.4%)	224 (97.0%)	2 (0.9%)	3 (1.3%)				
	HIGH ($> 1 \times \text{ULN}$ - < 5.5 MMOL/L)	4	0	0	4 (100.0%)	0	0				
	HIGH CONCERN (≥ 5.5 MMOL/L)	3	0	0	3 (100.0%)	0	0				
	MISSING	1	0	0	1 (100.0%)	0	0				
	TOTAL	239	1 (0.4%)	1 (0.4%)	232 (97.1%)	2 (0.8%)	3 (1.3%)				
SB 207499	LOW CONCERN (≤ 3.0 MMOL/L)	0	0	0	0	0	0				
	LOW (> 3.0 MMOL/L- $< 1 \times \text{LLN}$)	0	0	0	0	0	0				
	NORMAL ($1 \times \text{LLN}$ - $1 \times \text{ULN}$)	451	2 (0.4%)	437 (96.9%)	7 (1.6%)	5 (1.1%)					
	HIGH ($> 1 \times \text{ULN}$ - < 5.5 MMOL/L)	3	0	0	3 (100.0%)	0	0				
	HIGH CONCERN (≥ 5.5 MMOL/L)	14	0	0	11 (78.6%)	2 (14.3%)	1 (7.1%)				
	MISSING	4	0	0	4 (100.0%)	0	0				
	TOTAL	472	2 (0.4%)	455 (96.4%)	9 (1.9%)	6 (1.3%)					
TOTAL	LOW CONCERN (≤ 3.0 MMOL/L)	0	0	0	0	0	0				
	LOW (> 3.0 MMOL/L- $< 1 \times \text{LLN}$)	0	0	0	0	0	0				
	NORMAL ($1 \times \text{LLN}$ - $1 \times \text{ULN}$)	682	1 (0.1%)	3 (0.4%)	661 (96.9%)	9 (1.3%)	8 (1.2%)				
	HIGH ($> 1 \times \text{ULN}$ - < 5.5 MMOL/L)	7	0	0	7 (100.0%)	0	0				
	HIGH CONCERN (≥ 5.5 MMOL/L)	17	0	0	14 (82.4%)	2 (11.8%)	1 (5.9%)				
	MISSING	5	0	0	5 (100.0%)	0	0				
	TOTAL	711	1 (0.1%)	3 (0.4%)	687 (96.6%)	11 (1.5%)	9 (1.3%)				

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CHLORIDE TIME POINT: TOTAL ON-THERAPY

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			LOW		NORMAL		HIGH	

PLACEBO	LOW (<1xLLN)	4	4	(100.0%)	0		0	
	NORMAL (1xLLN-1xULN)	216	20	(9.3%)	134	(62.0%)	63	(29.2%)
	HIGH (>1xULN)	19	1	(5.3%)	5	(26.3%)	14	(73.7%)
	MISSING	0	0		0		0	
	TOTAL	239	25	(10.5%)	139	(58.2%)	77	(32.2%)
SB 207499	LOW (<1xLLN)	5	3	(60.0%)	1	(20.0%)	1	(20.0%)
	NORMAL (1xLLN-1xULN)	439	36	(8.2%)	272	(62.0%)	137	(31.2%)
	HIGH (>1xULN)	24	0		11	(45.8%)	13	(54.2%)
	MISSING	4	0		3	(75.0%)	1	(25.0%)
	TOTAL	472	39	(8.3%)	287	(60.8%)	152	(32.2%)
TOTAL	LOW (<1xLLN)	9	7	(77.8%)	1	(11.1%)	1	(11.1%)
	NORMAL (1xLLN-1xULN)	655	56	(8.5%)	406	(62.0%)	200	(30.5%)
	HIGH (>1xULN)	43	1	(2.3%)	16	(37.2%)	27	(62.8%)
	MISSING	4	0		3	(75.0%)	1	(25.0%)
	TOTAL	711	64	(9.0%)	426	(59.9%)	229	(32.2%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CHLORIDE TIME POINT: ENDPOINT

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			LOW		NORMAL		HIGH	

PLACEBO	LOW (<1xLLN)	4	1	(25.0%)	3	(75.0%)	0	
	NORMAL (1xLLN-1xULN)	216	3	(1.4%)	201	(93.1%)	12	(5.6%)
	HIGH (>1xULN)	19	0		17	(89.5%)	2	(10.5%)
	MISSING	0	0		0		0	
	TOTAL	239	4	(1.7%)	221	(92.5%)	14	(5.9%)
SB 207499	LOW (<1xLLN)	5	1	(20.0%)	3	(60.0%)	1	(20.0%)
	NORMAL (1xLLN-1xULN)	439	6	(1.4%)	409	(93.2%)	24	(5.5%)
	HIGH (>1xULN)	24	0		17	(70.8%)	7	(29.2%)
	MISSING	4	0		4	(100.0%)	0	
	TOTAL	472	7	(1.5%)	433	(91.7%)	32	(6.8%)
TOTAL	LOW (<1xLLN)	9	2	(22.2%)	6	(66.7%)	1	(11.1%)
	NORMAL (1xLLN-1xULN)	655	9	(1.4%)	610	(93.1%)	36	(5.5%)
	HIGH (>1xULN)	43	0		34	(79.1%)	9	(20.9%)
	MISSING	4	0		4	(100.0%)	0	
	TOTAL	711	11	(1.5%)	654	(92.0%)	46	(6.5%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

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TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: BLOOD UREA NITROGEN		TIME POINT: TOTAL ON-THERAPY					
PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL ($\leq 1 \times \text{ULN}$)	234	206	(88.0%)	28	(12.0%)	0
	HIGH ($> 1 \times \text{ULN} - 17.85 \text{ MMOL/L}$)	4	1	(25.0%)	3	(75.0%)	0
	CONCERN ($> 17.85 \text{ MMOL/L}$)	0	0		0		0
	MISSING	0	0		0		0
	TOTAL	238	207	(87.0%)	31	(13.0%)	0
SB 207499	NORMAL ($\leq 1 \times \text{ULN}$)	458	404	(88.2%)	53	(11.6%)	1 (0.2%)
	HIGH ($> 1 \times \text{ULN} - 17.85 \text{ MMOL/L}$)	9	2	(22.2%)	7	(77.8%)	0
	CONCERN ($> 17.85 \text{ MMOL/L}$)	1	0		0		1 (100.0%)
	MISSING	4	3	(75.0%)	1	(25.0%)	0
	TOTAL	472	409	(86.7%)	61	(12.9%)	2 (0.4%)
TOTAL	NORMAL ($\leq 1 \times \text{ULN}$)	692	610	(88.2%)	81	(11.7%)	1 (0.1%)
	HIGH ($> 1 \times \text{ULN} - 17.85 \text{ MMOL/L}$)	13	3	(23.1%)	10	(76.9%)	0
	CONCERN ($> 17.85 \text{ MMOL/L}$)	1	0		0		1 (100.0%)
	MISSING	4	3	(75.0%)	1	(25.0%)	0
	TOTAL	710	616	(86.8%)	92	(13.0%)	2 (0.3%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

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TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

		PARAMETER: BLOOD UREA NITROGEN		TIME POINT: ENDPOINT			
PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN

PLACEBO	NORMAL ($\leq 1 \times \text{ULN}$)	234	230	(98.3%)	4	(1.7%)	0
	HIGH ($> 1 \times \text{ULN} - 17.85 \text{ MMOL/L}$)	4	3	(75.0%)	1	(25.0%)	0
	CONCERN ($> 17.85 \text{ MMOL/L}$)	0	0		0		0
	MISSING	0	0		0		0
	TOTAL	238	233	(97.9%)	5	(2.1%)	0
SB 207499	NORMAL ($\leq 1 \times \text{ULN}$)	458	454	(99.1%)	4	(0.9%)	0
	HIGH ($> 1 \times \text{ULN} - 17.85 \text{ MMOL/L}$)	9	5	(55.6%)	4	(44.4%)	0
	CONCERN ($> 17.85 \text{ MMOL/L}$)	1	0		1	(100.0%)	0
	MISSING	4	4	(100.0%)	0		0
	TOTAL	472	463	(98.1%)	9	(1.9%)	0
TOTAL	NORMAL ($\leq 1 \times \text{ULN}$)	692	684	(98.8%)	8	(1.2%)	0
	HIGH ($> 1 \times \text{ULN} - 17.85 \text{ MMOL/L}$)	13	8	(61.5%)	5	(38.5%)	0
	CONCERN ($> 17.85 \text{ MMOL/L}$)	1	0		1	(100.0%)	0
	MISSING	4	4	(100.0%)	0		0
	TOTAL	710	696	(98.0%)	14	(2.0%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

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TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CREATININE TIME POINT: TOTAL ON-THERAPY

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----								
			LOW CONCERN		LOW		NORMAL		HIGH		HIGH CONCERN

PLACEBO	LOW CONCERN (<0.5xLLN)	0	0		0		0		0		0
	LOW (0.5xLLN-<1xLLN)	4	1 (25.0%)		3 (75.0%)		0		0		0
	NORMAL (1xLLN-1xULN)	230	1 (0.4%)		27 (11.7%)		182 (79.1%)		20 (8.7%)		0
	HIGH (>1xULN-1.5xULN)	4	0		0		0		4 (100.0%)		0
	HIGH CONCERN (>1.5xULN)	0	0		0		0		0		0
	MISSING	0	0		0		0		0		0
	TOTAL	238	2 (0.8%)		30 (12.6%)		182 (76.5%)		24 (10.1%)		0
SB 207499	LOW CONCERN (<0.5xLLN)	0	0		0		0		0		0
	LOW (0.5xLLN-<1xLLN)	9	0		7 (77.8%)		2 (22.2%)		0		0
	NORMAL (1xLLN-1xULN)	449	0		58 (12.9%)		363 (80.8%)		25 (5.6%)		3 (0.7%)
	HIGH (>1xULN-1.5xULN)	9	0		0		1 (11.1%)		8 (88.9%)		0
	HIGH CONCERN (>1.5xULN)	1	0		0		0		0		1 (100.0%)
	MISSING	4	0		0		4 (100.0%)		0		0
	TOTAL	472	0		65 (13.8%)		370 (78.4%)		33 (7.0%)		4 (0.8%)
TOTAL	LOW CONCERN (<0.5xLLN)	0	0		0		0		0		0
	LOW (0.5xLLN-<1xLLN)	13	1 (7.7%)		10 (76.9%)		2 (15.4%)		0		0
	NORMAL (1xLLN-1xULN)	679	1 (0.1%)		85 (12.5%)		545 (80.3%)		45 (6.6%)		3 (0.4%)
	HIGH (>1xULN-1.5xULN)	13	0		0		1 (7.7%)		12 (92.3%)		0
	HIGH CONCERN (>1.5xULN)	1	0		0		0		0		1 (100.0%)
	MISSING	4	0		0		4 (100.0%)		0		0
	TOTAL	710	2 (0.3%)		95 (13.4%)		552 (77.7%)		57 (8.0%)		4 (0.6%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

		PARAMETER: CREATININE	TIME POINT: ENDPOINT								
PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	LOW CONCERN	LOW	-ON-THERAPY-		NORMAL	HIGH	HIGH CONCERN		

PLACEBO	LOW CONCERN (<0.5xLLN)	0	0	0		0		0		0	
	LOW (0.5xLLN-<1xLLN)	4	0	2	(50.0%)	2	(50.0%)	0		0	
	NORMAL (1xLLN-1xULN)	230	0	8	(3.5%)	220	(95.7%)	2	(0.9%)	0	
	HIGH (>1xULN-1.5xULN)	4	0	0		0		4	(100.0%)	0	
	HIGH CONCERN (>1.5xULN)	0	0	0		0		0		0	
	MISSING	0	0	0		0		0		0	
	TOTAL	238	0	10	(4.2%)	222	(93.3%)	6	(2.5%)	0	
SB 207499	LOW CONCERN (<0.5xLLN)	0	0	0		0		0		0	
	LOW (0.5xLLN-<1xLLN)	9	0	4	(44.4%)	5	(55.6%)	0		0	
	NORMAL (1xLLN-1xULN)	449	0	5	(1.1%)	439	(97.8%)	5	(1.1%)	0	
	HIGH (>1xULN-1.5xULN)	9	0	0		5	(55.6%)	4	(44.4%)	0	
	HIGH CONCERN (>1.5xULN)	1	0	0		0		0		1 (100.0%)	
	MISSING	4	0	0		4	(100.0%)	0		0	
	TOTAL	472	0	9	(1.9%)	453	(96.0%)	9	(1.9%)	1 (0.2%)	
TOTAL	LOW CONCERN (<0.5xLLN)	0	0	0		0		0		0	
	LOW (0.5xLLN-<1xLLN)	13	0	6	(46.2%)	7	(53.8%)	0		0	
	NORMAL (1xLLN-1xULN)	679	0	13	(1.9%)	659	(97.1%)	7	(1.0%)	0	
	HIGH (>1xULN-1.5xULN)	13	0	0		5	(38.5%)	8	(61.5%)	0	
	HIGH CONCERN (>1.5xULN)	1	0	0		0		0		1 (100.0%)	
	MISSING	4	0	0		4	(100.0%)	0		0	
	TOTAL	710	0	19	(2.7%)	675	(95.1%)	15	(2.1%)	1 (0.1%)	

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: URIC ACID TIME POINT: TOTAL ON-THERAPY

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL ($\leq 1 \times \text{ULN}$)	233	211	(90.6%)	20	(8.6%)	2	(0.9%)
	HIGH ($> 1 \times \text{ULN} - 1.4 \times \text{ULN}$)	5	1	(20.0%)	4	(80.0%)	0	
	CONCERN ($> 1.4 \times \text{ULN}$)	0	0		0		0	
	MISSING	0	0		0		0	
	TOTAL	238	212	(89.1%)	24	(10.1%)	2	(0.8%)
SB 207499	NORMAL ($\leq 1 \times \text{ULN}$)	458	418	(91.3%)	40	(8.7%)	0	
	HIGH ($> 1 \times \text{ULN} - 1.4 \times \text{ULN}$)	10	4	(40.0%)	6	(60.0%)	0	
	CONCERN ($> 1.4 \times \text{ULN}$)	0	0		0		0	
	MISSING	4	4	(100.0%)	0		0	
	TOTAL	472	426	(90.3%)	46	(9.7%)	0	
TOTAL	NORMAL ($\leq 1 \times \text{ULN}$)	691	629	(91.0%)	60	(8.7%)	2	(0.3%)
	HIGH ($> 1 \times \text{ULN} - 1.4 \times \text{ULN}$)	15	5	(33.3%)	10	(66.7%)	0	
	CONCERN ($> 1.4 \times \text{ULN}$)	0	0		0		0	
	MISSING	4	4	(100.0%)	0		0	
	TOTAL	710	638	(89.9%)	70	(9.9%)	2	(0.3%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

		PARAMETER: URIC ACID		TIME POINT: ENDPOINT			
PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	NORMAL		ON-THERAPY		CONCERN
			-----		-----		
PLACEBO	NORMAL ($\leq 1 \times \text{ULN}$)	233	229	(98.3%)	3	(1.3%)	1 (0.4%)
	HIGH ($> 1 \times \text{ULN} - 1.4 \times \text{ULN}$)	5	3	(60.0%)	2	(40.0%)	0
	CONCERN ($> 1.4 \times \text{ULN}$)	0	0		0		0
	MISSING	0	0		0		0
	TOTAL	238	232	(97.5%)	5	(2.1%)	1 (0.4%)
SB 207499	NORMAL ($\leq 1 \times \text{ULN}$)	458	446	(97.4%)	12	(2.6%)	0
	HIGH ($> 1 \times \text{ULN} - 1.4 \times \text{ULN}$)	10	7	(70.0%)	3	(30.0%)	0
	CONCERN ($> 1.4 \times \text{ULN}$)	0	0		0		0
	MISSING	4	4	(100.0%)	0		0
	TOTAL	472	457	(96.8%)	15	(3.2%)	0
TOTAL	NORMAL ($\leq 1 \times \text{ULN}$)	691	675	(97.7%)	15	(2.2%)	1 (0.1%)
	HIGH ($> 1 \times \text{ULN} - 1.4 \times \text{ULN}$)	15	10	(66.7%)	5	(33.3%)	0
	CONCERN ($> 1.4 \times \text{ULN}$)	0	0		0		0
	MISSING	4	4	(100.0%)	0		0
	TOTAL	710	689	(97.0%)	20	(2.8%)	1 (0.1%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ALKALINE PHOSPHATASE			TIME POINT: TOTAL ON-THERAPY			
PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		HIGH	CONCERN

PLACEBO	NORMAL (<=1xULN)	231	222	(96.1%)	9	(3.9%)
	HIGH (>1xULN-2xULN)	6	1	(16.7%)	5	(83.3%)
	CONCERN (>2xULN)	0	0		0	
	MISSING	1	1	(100.0%)	0	
	TOTAL	238	224	(94.1%)	14	(5.9%)
SB 207499	NORMAL (<=1xULN)	456	425	(93.2%)	31	(6.8%)
	HIGH (>1xULN-2xULN)	12	2	(16.7%)	10	(83.3%)
	CONCERN (>2xULN)	0	0		0	
	MISSING	4	4	(100.0%)	0	
	TOTAL	472	431	(91.3%)	41	(8.7%)
TOTAL	NORMAL (<=1xULN)	687	647	(94.2%)	40	(5.8%)
	HIGH (>1xULN-2xULN)	18	3	(16.7%)	15	(83.3%)
	CONCERN (>2xULN)	0	0		0	
	MISSING	5	5	(100.0%)	0	
	TOTAL	710	655	(92.3%)	55	(7.7%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ALKALINE PHOSPHATASE TIME POINT: ENDPOINT

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL ($\leq 1 \times \text{ULN}$)	231	228	(98.7%)	3	(1.3%)	0
	HIGH ($> 1 \times \text{ULN} - 2 \times \text{ULN}$)	6	4	(66.7%)	2	(33.3%)	0
	CONCERN ($> 2 \times \text{ULN}$)	0	0		0		0
	MISSING	1	1	(100.0%)	0		0
	TOTAL	238	233	(97.9%)	5	(2.1%)	0
SB 207499	NORMAL ($\leq 1 \times \text{ULN}$)	456	446	(97.8%)	10	(2.2%)	0
	HIGH ($> 1 \times \text{ULN} - 2 \times \text{ULN}$)	12	4	(33.3%)	8	(66.7%)	0
	CONCERN ($> 2 \times \text{ULN}$)	0	0		0		0
	MISSING	4	4	(100.0%)	0		0
	TOTAL	472	454	(96.2%)	18	(3.8%)	0
TOTAL	NORMAL ($\leq 1 \times \text{ULN}$)	687	674	(98.1%)	13	(1.9%)	0
	HIGH ($> 1 \times \text{ULN} - 2 \times \text{ULN}$)	18	8	(44.4%)	10	(55.6%)	0
	CONCERN ($> 2 \times \text{ULN}$)	0	0		0		0
	MISSING	5	5	(100.0%)	0		0
	TOTAL	710	687	(96.8%)	23	(3.2%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

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TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ASPARTATE AMINOTRANSFERASE TIME POINT: TOTAL ON-THERAPY

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL ($\leq 1 \times \text{ULN}$)	230	217	(94.3%)	11	(4.8%)	2	(0.9%)
	HIGH ($> 1 \times \text{ULN} - 2 \times \text{ULN}$)	7	2	(28.6%)	2	(28.6%)	3	(42.9%)
	CONCERN ($> 2 \times \text{ULN}$)	0	0		0		0	
	MISSING	1	1	(100.0%)	0		0	
	TOTAL	238	220	(92.4%)	13	(5.5%)	5	(2.1%)
SB 207499	NORMAL ($\leq 1 \times \text{ULN}$)	462	417	(90.3%)	35	(7.6%)	10	(2.2%)
	HIGH ($> 1 \times \text{ULN} - 2 \times \text{ULN}$)	4	0		4	(100.0%)	0	
	CONCERN ($> 2 \times \text{ULN}$)	2	0		1	(50.0%)	1	(50.0%)
	MISSING	4	3	(75.0%)	1	(25.0%)	0	
	TOTAL	472	420	(89.0%)	41	(8.7%)	11	(2.3%)
TOTAL	NORMAL ($\leq 1 \times \text{ULN}$)	692	634	(91.6%)	46	(6.6%)	12	(1.7%)
	HIGH ($> 1 \times \text{ULN} - 2 \times \text{ULN}$)	11	2	(18.2%)	6	(54.5%)	3	(27.3%)
	CONCERN ($> 2 \times \text{ULN}$)	2	0		1	(50.0%)	1	(50.0%)
	MISSING	5	4	(80.0%)	1	(20.0%)	0	
	TOTAL	710	640	(90.1%)	54	(7.6%)	16	(2.3%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ASPARTATE AMINOTRANSFERASE TIME POINT: ENDPOINT

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL ($\leq 1 \times \text{ULN}$)	230	226	(98.3%)	3	(1.3%)	1	(0.4%)
	HIGH ($> 1 \times \text{ULN} - 2 \times \text{ULN}$)	7	3	(42.9%)	4	(57.1%)	0	
	CONCERN ($> 2 \times \text{ULN}$)	0	0		0		0	
	MISSING	1	1	(100.0%)	0		0	
	TOTAL	238	230	(96.6%)	7	(2.9%)	1	(0.4%)
SB 207499	NORMAL ($\leq 1 \times \text{ULN}$)	462	451	(97.6%)	11	(2.4%)	0	
	HIGH ($> 1 \times \text{ULN} - 2 \times \text{ULN}$)	4	2	(50.0%)	2	(50.0%)	0	
	CONCERN ($> 2 \times \text{ULN}$)	2	1	(50.0%)	1	(50.0%)	0	
	MISSING	4	4	(100.0%)	0		0	
	TOTAL	472	458	(97.0%)	14	(3.0%)	0	
TOTAL	NORMAL ($\leq 1 \times \text{ULN}$)	692	677	(97.8%)	14	(2.0%)	1	(0.1%)
	HIGH ($> 1 \times \text{ULN} - 2 \times \text{ULN}$)	11	5	(45.5%)	6	(54.5%)	0	
	CONCERN ($> 2 \times \text{ULN}$)	2	1	(50.0%)	1	(50.0%)	0	
	MISSING	5	5	(100.0%)	0		0	
	TOTAL	710	688	(96.9%)	21	(3.0%)	1	(0.1%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ALANINE AMINOTRANSFERASE TIME POINT: TOTAL ON-THERAPY

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL ($\leq 1 \times \text{ULN}$)	227	206	(90.7%)	21	(9.3%)	0	
	HIGH ($> 1 \times \text{ULN} - 2 \times \text{ULN}$)	9	4	(44.4%)	3	(33.3%)	2	(22.2%)
	CONCERN ($> 2 \times \text{ULN}$)	1	0		1	(100.0%)	0	
	MISSING	1	1	(100.0%)	0		0	
	TOTAL	238	211	(88.7%)	25	(10.5%)	2	(0.8%)
SB 207499	NORMAL ($\leq 1 \times \text{ULN}$)	455	402	(88.4%)	40	(8.8%)	13	(2.9%)
	HIGH ($> 1 \times \text{ULN} - 2 \times \text{ULN}$)	12	3	(25.0%)	8	(66.7%)	1	(8.3%)
	CONCERN ($> 2 \times \text{ULN}$)	1	0		0		1	(100.0%)
	MISSING	4	3	(75.0%)	1	(25.0%)	0	
	TOTAL	472	408	(86.4%)	49	(10.4%)	15	(3.2%)
TOTAL	NORMAL ($\leq 1 \times \text{ULN}$)	682	608	(89.1%)	61	(8.9%)	13	(1.9%)
	HIGH ($> 1 \times \text{ULN} - 2 \times \text{ULN}$)	21	7	(33.3%)	11	(52.4%)	3	(14.3%)
	CONCERN ($> 2 \times \text{ULN}$)	2	0		1	(50.0%)	1	(50.0%)
	MISSING	5	4	(80.0%)	1	(20.0%)	0	
	TOTAL	710	619	(87.2%)	74	(10.4%)	17	(2.4%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

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TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ALANINE AMINOTRANSFERASE TIME POINT: ENDPOINT

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL	HIGH	CONCERN	
PLACEBO	NORMAL ($\leq 1 \times \text{ULN}$)	227	224 (98.7%)	3 (1.3%)	0	
	HIGH ($> 1 \times \text{ULN} - 2 \times \text{ULN}$)	9	5 (55.6%)	4 (44.4%)	0	
	CONCERN ($> 2 \times \text{ULN}$)	1	0	1 (100.0%)	0	
	MISSING	1	1 (100.0%)	0	0	
	TOTAL	238	230 (96.6%)	8 (3.4%)	0	
SB 207499	NORMAL ($\leq 1 \times \text{ULN}$)	455	445 (97.8%)	9 (2.0%)	1 (0.2%)	
	HIGH ($> 1 \times \text{ULN} - 2 \times \text{ULN}$)	12	8 (66.7%)	4 (33.3%)	0	
	CONCERN ($> 2 \times \text{ULN}$)	1	1 (100.0%)	0	0	
	MISSING	4	4 (100.0%)	0	0	
	TOTAL	472	458 (97.0%)	13 (2.8%)	1 (0.2%)	
TOTAL	NORMAL ($\leq 1 \times \text{ULN}$)	682	669 (98.1%)	12 (1.8%)	1 (0.1%)	
	HIGH ($> 1 \times \text{ULN} - 2 \times \text{ULN}$)	21	13 (61.9%)	8 (38.1%)	0	
	CONCERN ($> 2 \times \text{ULN}$)	2	1 (50.0%)	1 (50.0%)	0	
	MISSING	5	5 (100.0%)	0	0	
	TOTAL	710	688 (96.9%)	21 (3.0%)	1 (0.1%)	

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: TOTAL BILIRUBIN TIME POINT: TOTAL ON-THERAPY

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL ($\leq 1 \times \text{ULN}$)	234	201	(85.9%)	28	(12.0%)	5	(2.1%)
	HIGH ($> 1 \times \text{ULN} - 1.5 \times \text{ULN}$)	4	1	(25.0%)	1	(25.0%)	2	(50.0%)
	CONCERN ($> 1.5 \times \text{ULN}$)	0	0		0		0	
	MISSING	0	0		0		0	
	TOTAL	238	202	(84.9%)	29	(12.2%)	7	(2.9%)
SB 207499	NORMAL ($\leq 1 \times \text{ULN}$)	453	396	(87.4%)	49	(10.8%)	8	(1.8%)
	HIGH ($> 1 \times \text{ULN} - 1.5 \times \text{ULN}$)	13	1	(7.7%)	5	(38.5%)	7	(53.8%)
	CONCERN ($> 1.5 \times \text{ULN}$)	2	0		0		2	(100.0%)
	MISSING	4	4	(100.0%)	0		0	
	TOTAL	472	401	(85.0%)	54	(11.4%)	17	(3.6%)
TOTAL	NORMAL ($\leq 1 \times \text{ULN}$)	687	597	(86.9%)	77	(11.2%)	13	(1.9%)
	HIGH ($> 1 \times \text{ULN} - 1.5 \times \text{ULN}$)	17	2	(11.8%)	6	(35.3%)	9	(52.9%)
	CONCERN ($> 1.5 \times \text{ULN}$)	2	0		0		2	(100.0%)
	MISSING	4	4	(100.0%)	0		0	
	TOTAL	710	603	(84.9%)	83	(11.7%)	24	(3.4%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

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TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: TOTAL BILIRUBIN		TIME POINT: ENDPOINT					
PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL ($\leq 1 \times \text{ULN}$)	234	229	(97.9%)	4	(1.7%)	1 (0.4%)
	HIGH ($> 1 \times \text{ULN} - 1.5 \times \text{ULN}$)	4	1	(25.0%)	1	(25.0%)	2 (50.0%)
	CONCERN ($> 1.5 \times \text{ULN}$)	0	0		0		0
	MISSING	0	0		0		0
	TOTAL	238	230	(96.6%)	5	(2.1%)	3 (1.3%)
SB 207499	NORMAL ($\leq 1 \times \text{ULN}$)	453	447	(98.7%)	6	(1.3%)	0
	HIGH ($> 1 \times \text{ULN} - 1.5 \times \text{ULN}$)	13	6	(46.2%)	6	(46.2%)	1 (7.7%)
	CONCERN ($> 1.5 \times \text{ULN}$)	2	0		2	(100.0%)	0
	MISSING	4	4	(100.0%)	0		0
	TOTAL	472	457	(96.8%)	14	(3.0%)	1 (0.2%)
TOTAL	NORMAL ($\leq 1 \times \text{ULN}$)	687	676	(98.4%)	10	(1.5%)	1 (0.1%)
	HIGH ($> 1 \times \text{ULN} - 1.5 \times \text{ULN}$)	17	7	(41.2%)	7	(41.2%)	3 (17.6%)
	CONCERN ($> 1.5 \times \text{ULN}$)	2	0		2	(100.0%)	0
	MISSING	4	4	(100.0%)	0		0
	TOTAL	710	687	(96.8%)	19	(2.7%)	4 (0.6%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: TOTAL PROTEIN TIME POINT: TOTAL ON-THERAPY

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			LOW	NORMAL	HIGH	
PLACEBO	LOW (<1xLLN)	0	0	0	0	
	NORMAL (1xLLN-1xULN)	237	7 (3.0%)	222 (93.7%)	8 (3.4%)	
	HIGH (>1xULN)	1	0	0	1 (100.0%)	
	MISSING	0	0	0	0	
	TOTAL	238	7 (2.9%)	222 (93.3%)	9 (3.8%)	
SB 207499	LOW (<1xLLN)	0	0	0	0	
	NORMAL (1xLLN-1xULN)	459	12 (2.6%)	433 (94.3%)	14 (3.1%)	
	HIGH (>1xULN)	9	0	2 (22.2%)	7 (77.8%)	
	MISSING	4	0	4 (100.0%)	0	
	TOTAL	472	12 (2.5%)	439 (93.0%)	21 (4.4%)	
TOTAL	LOW (<1xLLN)	0	0	0	0	
	NORMAL (1xLLN-1xULN)	696	19 (2.7%)	655 (94.1%)	22 (3.2%)	
	HIGH (>1xULN)	10	0	2 (20.0%)	8 (80.0%)	
	MISSING	4	0	4 (100.0%)	0	
	TOTAL	710	19 (2.7%)	661 (93.1%)	30 (4.2%)	

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: TOTAL PROTEIN TIME POINT: ENDPOINT

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			LOW	NORMAL	HIGH	
PLACEBO	LOW (<1xLLN)	0	0	0	0	
	NORMAL (1xLLN-1xULN)	237	2 (0.8%)	234 (98.7%)	1 (0.4%)	
	HIGH (>1xULN)	1	0	1 (100.0%)	0	
	MISSING	0	0	0	0	
	TOTAL	238	2 (0.8%)	235 (98.7%)	1 (0.4%)	
SB 207499	LOW (<1xLLN)	0	0	0	0	
	NORMAL (1xLLN-1xULN)	459	1 (0.2%)	458 (99.8%)	0	
	HIGH (>1xULN)	9	0	8 (88.9%)	1 (11.1%)	
	MISSING	4	0	4 (100.0%)	0	
	TOTAL	472	1 (0.2%)	470 (99.6%)	1 (0.2%)	
TOTAL	LOW (<1xLLN)	0	0	0	0	
	NORMAL (1xLLN-1xULN)	696	3 (0.4%)	692 (99.4%)	1 (0.1%)	
	HIGH (>1xULN)	10	0	9 (90.0%)	1 (10.0%)	
	MISSING	4	0	4 (100.0%)	0	
	TOTAL	710	3 (0.4%)	705 (99.3%)	2 (0.3%)	

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ALBUMIN TIME POINT: TOTAL ON-THERAPY

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			LOW	NORMAL	HIGH	
PLACEBO	LOW (<1xLLN)	0	0	0	0	
	NORMAL (1xLLN-1xULN)	238	0	237 (99.6%)	1 (0.4%)	
	HIGH (>1xULN)	0	0	0	0	
	MISSING	0	0	0	0	
	TOTAL	238	0	237 (99.6%)	1 (0.4%)	
SB 207499	LOW (<1xLLN)	0	0	0	0	
	NORMAL (1xLLN-1xULN)	468	3 (0.6%)	464 (99.1%)	1 (0.2%)	
	HIGH (>1xULN)	0	0	0	0	
	MISSING	4	0	4 (100.0%)	0	
	TOTAL	472	3 (0.6%)	468 (99.2%)	1 (0.2%)	
TOTAL	LOW (<1xLLN)	0	0	0	0	
	NORMAL (1xLLN-1xULN)	706	3 (0.4%)	701 (99.3%)	2 (0.3%)	
	HIGH (>1xULN)	0	0	0	0	
	MISSING	4	0	4 (100.0%)	0	
	TOTAL	710	3 (0.4%)	705 (99.3%)	2 (0.3%)	

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ALBUMIN TIME POINT: ENDPOINT

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----		
			LOW	NORMAL	HIGH
PLACEBO	LOW (<1xLLN)	0	0	0	0
	NORMAL (1xLLN-1xULN)	238	0	238 (100.0%)	0
	HIGH (>1xULN)	0	0	0	0
	MISSING	0	0	0	0
	TOTAL	238	0	238 (100.0%)	0
SB 207499	LOW (<1xLLN)	0	0	0	0
	NORMAL (1xLLN-1xULN)	468	0	468 (100.0%)	0
	HIGH (>1xULN)	0	0	0	0
	MISSING	4	0	4 (100.0%)	0
	TOTAL	472	0	472 (100.0%)	0
TOTAL	LOW (<1xLLN)	0	0	0	0
	NORMAL (1xLLN-1xULN)	706	0	706 (100.0%)	0
	HIGH (>1xULN)	0	0	0	0
	MISSING	4	0	4 (100.0%)	0
	TOTAL	710	0	710 (100.0%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: GLUCOSE - RANDOM TIME POINT: TOTAL ON-THERAPY

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----									
			LOW CONCERN		LOW		NORMAL		HIGH		HIGH CONCERN	

PLACEBO	LOW CONCERN (<2.0 MMOL/L)	0	0		0		0		0			
	LOW (2.0 MMOL/L-<1xLLN)	3	0		1	(33.3%)	1	(33.3%)	1	(33.3%)	1	(33.3%)
	NORMAL (1xLLN-1xULN)	190	3	(1.6%)	30	(15.8%)	59	(31.1%)	50	(26.3%)	68	(35.8%)
	HIGH (>1xULN-8.0 MMOL/L)	20	0		1	(5.0%)	0		6	(30.0%)	14	(70.0%)
	HIGH CONCERN (>8.0 MMOL/L)	24	0		1	(4.2%)	3	(12.5%)	3	(12.5%)	17	(70.8%)
	MISSING	1	0		0		1	(100.0%)	0		0	
	TOTAL	238	3	(1.3%)	33	(13.9%)	64	(26.9%)	60	(25.2%)	100	(42.0%)

SB 207499	LOW CONCERN (<2.0 MMOL/L)	0	0		0		0		0		0	
	LOW (2.0 MMOL/L-<1xLLN)	12	1	(8.3%)	9	(75.0%)	0		4	(33.3%)	2	(16.7%)
	NORMAL (1xLLN-1xULN)	375	4	(1.1%)	75	(20.0%)	128	(34.1%)	89	(23.7%)	121	(32.3%)
	HIGH (>1xULN-8.0 MMOL/L)	34	0		6	(17.6%)	3	(8.8%)	10	(29.4%)	20	(58.8%)
	HIGH CONCERN (>8.0 MMOL/L)	47	0		4	(8.5%)	2	(4.3%)	3	(6.4%)	42	(89.4%)
	MISSING	4	1	(25.0%)	0		1	(25.0%)	1	(25.0%)	2	(50.0%)
	TOTAL	472	6	(1.3%)	94	(19.9%)	134	(28.4%)	107	(22.7%)	187	(39.6%)

TOTAL	LOW CONCERN (<2.0 MMOL/L)	0	0		0		0		0		0	
	LOW (2.0 MMOL/L-<1xLLN)	15	1	(6.7%)	10	(66.7%)	1	(6.7%)	5	(33.3%)	3	(20.0%)
	NORMAL (1xLLN-1xULN)	565	7	(1.2%)	105	(18.6%)	187	(33.1%)	139	(24.6%)	189	(33.5%)
	HIGH (>1xULN-8.0 MMOL/L)	54	0		7	(13.0%)	3	(5.6%)	16	(29.6%)	34	(63.0%)
	HIGH CONCERN (>8.0 MMOL/L)	71	0		5	(7.0%)	5	(7.0%)	6	(8.5%)	59	(83.1%)
	MISSING	5	1	(20.0%)	0		2	(40.0%)	1	(20.0%)	2	(40.0%)
	TOTAL	710	9	(1.3%)	127	(17.9%)	198	(27.9%)	167	(23.5%)	287	(40.4%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

		PARAMETER: GLUCOSE - RANDOM		TIME POINT: ENDPOINT							
PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	LOW CONCERN	LOW	-----ON-THERAPY-----		HIGH	HIGH CONCERN			

PLACEBO	LOW CONCERN (<2.0 MMOL/L)	0	0	0	0		0		0		
	LOW (2.0 MMOL/L-<1xLLN)	3	0	0	3	(100.0%)	0		0		
	NORMAL (1xLLN-1xULN)	190	0	3	(1.6%)	157	(82.6%)	17	(8.9%)	13	(6.8%)
	HIGH (>1xULN-8.0 MMOL/L)	20	0	0		13	(65.0%)	3	(15.0%)	4	(20.0%)
	HIGH CONCERN (>8.0 MMOL/L)	24	0	0		13	(54.2%)	0		11	(45.8%)
	MISSING	1	0	0		1	(100.0%)	0		0	
	TOTAL	238	0	3	(1.3%)	187	(78.6%)	20	(8.4%)	28	(11.8%)
SB 207499	LOW CONCERN (<2.0 MMOL/L)	0	0	0	0		0		0		
	LOW (2.0 MMOL/L-<1xLLN)	12	0	3	(25.0%)	9	(75.0%)	0		0	
	NORMAL (1xLLN-1xULN)	375	0	9	(2.4%)	311	(82.9%)	28	(7.5%)	27	(7.2%)
	HIGH (>1xULN-8.0 MMOL/L)	34	0	1	(2.9%)	19	(55.9%)	6	(17.6%)	8	(23.5%)
	HIGH CONCERN (>8.0 MMOL/L)	47	0	0		16	(34.0%)	8	(17.0%)	23	(48.9%)
	MISSING	4	0	0		3	(75.0%)	0		1	(25.0%)
	TOTAL	472	0	13	(2.8%)	358	(75.8%)	42	(8.9%)	59	(12.5%)
TOTAL	LOW CONCERN (<2.0 MMOL/L)	0	0	0	0		0		0		
	LOW (2.0 MMOL/L-<1xLLN)	15	0	3	(20.0%)	12	(80.0%)	0		0	
	NORMAL (1xLLN-1xULN)	565	0	12	(2.1%)	468	(82.8%)	45	(8.0%)	40	(7.1%)
	HIGH (>1xULN-8.0 MMOL/L)	54	0	1	(1.9%)	32	(59.3%)	9	(16.7%)	12	(22.2%)
	HIGH CONCERN (>8.0 MMOL/L)	71	0	0		29	(40.8%)	8	(11.3%)	34	(47.9%)
	MISSING	5	0	0		4	(80.0%)	0		1	(20.0%)
	TOTAL	710	0	16	(2.3%)	545	(76.8%)	62	(8.7%)	87	(12.3%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: GAMMA GLUTAMYL TRANSFERASE TIME POINT: TOTAL ON-THERAPY

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL ($\leq 1 \times \text{ULN}$)	213	173	(81.2%)	36	(16.9%)	4	(1.9%)
	HIGH ($> 1 \times \text{ULN} - 2.5 \times \text{ULN}$)	22	2	(9.1%)	18	(81.8%)	2	(9.1%)
	CONCERN ($> 2.5 \times \text{ULN}$)	3	0		0		3	(100.0%)
	MISSING	0	0		0		0	
	TOTAL	238	175	(73.5%)	54	(22.7%)	9	(3.8%)
SB 207499	NORMAL ($\leq 1 \times \text{ULN}$)	401	332	(82.8%)	53	(13.2%)	16	(4.0%)
	HIGH ($> 1 \times \text{ULN} - 2.5 \times \text{ULN}$)	60	4	(6.7%)	35	(58.3%)	21	(35.0%)
	CONCERN ($> 2.5 \times \text{ULN}$)	7	0		2	(28.6%)	5	(71.4%)
	MISSING	4	1	(25.0%)	2	(50.0%)	1	(25.0%)
	TOTAL	472	337	(71.4%)	92	(19.5%)	43	(9.1%)
TOTAL	NORMAL ($\leq 1 \times \text{ULN}$)	614	505	(82.2%)	89	(14.5%)	20	(3.3%)
	HIGH ($> 1 \times \text{ULN} - 2.5 \times \text{ULN}$)	82	6	(7.3%)	53	(64.6%)	23	(28.0%)
	CONCERN ($> 2.5 \times \text{ULN}$)	10	0		2	(20.0%)	8	(80.0%)
	MISSING	4	1	(25.0%)	2	(50.0%)	1	(25.0%)
	TOTAL	710	512	(72.1%)	146	(20.6%)	52	(7.3%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

SB 207499

TABLE 15.15

TRANSITIONS FROM BASELINE IN LABORATORY VALUES BY ANALYTE BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: GAMMA GLUTAMYL TRANSFERASE TIME POINT: ENDPOINT

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL ($\leq 1 \times \text{ULN}$)	213	199	(93.4%)	12	(5.6%)	2	(0.9%)
	HIGH ($> 1 \times \text{ULN} - 2.5 \times \text{ULN}$)	22	12	(54.5%)	10	(45.5%)	0	
	CONCERN ($> 2.5 \times \text{ULN}$)	3	0		1	(33.3%)	2	(66.7%)
	MISSING	0	0		0		0	
	TOTAL	238	211	(88.7%)	23	(9.7%)	4	(1.7%)
SB 207499	NORMAL ($\leq 1 \times \text{ULN}$)	401	370	(92.3%)	28	(7.0%)	3	(0.7%)
	HIGH ($> 1 \times \text{ULN} - 2.5 \times \text{ULN}$)	60	24	(40.0%)	27	(45.0%)	9	(15.0%)
	CONCERN ($> 2.5 \times \text{ULN}$)	7	2	(28.6%)	1	(14.3%)	4	(57.1%)
	MISSING	4	2	(50.0%)	2	(50.0%)	0	
	TOTAL	472	398	(84.3%)	58	(12.3%)	16	(3.4%)
TOTAL	NORMAL ($\leq 1 \times \text{ULN}$)	614	569	(92.7%)	40	(6.5%)	5	(0.8%)
	HIGH ($> 1 \times \text{ULN} - 2.5 \times \text{ULN}$)	82	36	(43.9%)	37	(45.1%)	9	(11.0%)
	CONCERN ($> 2.5 \times \text{ULN}$)	10	2	(20.0%)	2	(20.0%)	6	(60.0%)
	MISSING	4	2	(50.0%)	2	(50.0%)	0	
	TOTAL	710	609	(85.8%)	81	(11.4%)	20	(2.8%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS CLINICAL LABORATORIES COLLECTED DURING EXTENSION PERIOD

SB 207499

TABLE 15.16

DESCRIPTIVE STATISTICS FOR STANDARD VITAL SIGNS BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Systolic BP (MM HG)	BASELINE	PLACEBO	243	135.2	17.1	100	184	0	.	.	.	.
		SB 207499	480	134.3	18.0	90	200	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	242	133.1	17.6	100	221	242	-2.1	15.9	-50	58
		SB 207499	479	131.6	17.1	89	198	479	-2.7	15.0	-50	50
	VISIT 2/WEEK 1	PLACEBO	237	132.5	16.4	90	192	237	-2.7	14.7	-40	45
		SB 207499	466	131.0	16.5	90	204	466	-3.2	16.0	-70	50
	VISIT 3/WEEK 2	PLACEBO	228	133.3	17.3	90	209	228	-2.1	15.7	-64	46
		SB 207499	460	131.8	15.9	85	205	460	-2.6	15.7	-68	50
	VISIT 4/WEEK 4	PLACEBO	219	133.3	16.7	90	190	219	-1.8	14.1	-40	40
		SB 207499	459	131.7	16.5	85	208	459	-2.7	16.0	-60	40
	VISIT 5/WEEK 8	PLACEBO	213	132.8	16.8	90	191	213	-2.1	15.2	-40	40
		SB 207499	451	131.7	16.8	92	210	451	-2.8	16.7	-70	48
	VISIT 6/WEEK 12	PLACEBO	207	133.5	16.6	100	181	207	-1.4	14.6	-36	42
		SB 207499	443	132.7	17.1	80	204	443	-1.9	16.0	-65	50
	VISIT 7/WEEK 16	PLACEBO	202	134.0	18.4	90	189	202	-0.7	15.8	-50	39
		SB 207499	438	132.9	16.3	95	196	438	-1.7	16.5	-60	46
	VISIT 8/WEEK 20	PLACEBO	197	132.9	16.4	90	186	197	-1.8	14.9	-40	50
		SB 207499	434	131.5	16.0	90	204	434	-3.1	16.4	-70	43
	VISIT 9/WEEK 24	PLACEBO	193	132.7	15.8	97	189	193	-2.1	14.6	-48	40
		SB 207499	428	131.7	16.7	80	190	428	-2.8	16.0	-85	48
	VISIT 10/WEEK 28	PLACEBO	191	131.2	16.9	85	180	191	-3.3	14.8	-65	40
		SB 207499	422	131.4	16.7	86	193	422	-3.1	16.3	-75	50
	VISIT 11/WEEK 32	PLACEBO	187	133.0	15.7	92	178	187	-1.3	14.3	-40	40
		SB 207499	419	133.1	17.7	86	200	419	-1.5	17.0	-70	85
	VISIT 12/WEEK 36	PLACEBO	187	132.7	16.5	85	183	187	-1.6	14.2	-40	42
		SB 207499	413	132.6	17.0	90	180	413	-2.1	16.1	-70	44
	VISIT 13/WEEK 40	PLACEBO	184	134.0	16.6	90	190	184	-0.3	15.8	-30	70
		SB 207499	407	132.5	16.7	92	200	407	-2.0	16.0	-70	53
	VISIT 14/WEEK 44	PLACEBO	184	132.0	16.3	90	190	184	-2.4	16.6	-40	45
		SB 207499	405	131.7	16.0	90	201	405	-2.9	16.9	-70	62

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.16

DESCRIPTIVE STATISTICS FOR STANDARD VITAL SIGNS BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Systolic BP (MM HG)	VISIT 15/WEEK 48	PLACEBO	184	131.9	15.0	90	170	184	-2.5	15.3	-42	45
		SB 207499	402	131.6	16.6	80	183	402	-2.9	15.5	-70	38
	VISIT 16/WEEK 52	PLACEBO	180	131.8	15.5	90	180	180	-2.5	15.5	-60	43
		SB 207499	386	131.4	16.3	90	190	386	-3.6	16.6	-70	40
	VISIT 17/WEEK 56	PLACEBO	172	132.4	16.0	100	174	172	-2.1	14.6	-35	40
		SB 207499	367	133.1	16.1	88	185	367	-1.7	16.5	-75	44
	VISIT 18/WEEK 60	PLACEBO	174	133.4	16.0	100	185	174	-0.8	15.5	-50	43
		SB 207499	374	131.7	16.5	80	191	374	-2.7	15.6	-60	54
	VISIT 19/WEEK 64	PLACEBO	142	131.5	16.8	90	188	142	-2.7	15.8	-40	40
		SB 207499	311	134.3	17.9	86	212	311	-1.4	17.5	-80	50
	VISIT 20/WEEK 68	PLACEBO	140	131.8	16.4	90	180	140	-2.3	15.3	-40	35
		SB 207499	299	134.9	17.1	90	194	299	-0.7	16.6	-45	41
	VISIT 21/WEEK 72	PLACEBO	171	131.4	16.8	90	185	171	-2.7	15.2	-40	40
		SB 207499	359	133.7	17.4	85	198	359	-0.4	16.3	-49	40
	VISIT 22/WEEK 76	PLACEBO	100	133.4	17.1	90	170	100	-1.4	14.7	-45	30
		SB 207499	199	133.8	18.5	90	196	199	-2.5	16.6	-49	40
	VISIT 23/WEEK 80	PLACEBO	98	132.1	18.2	90	180	98	-2.7	15.7	-50	40
		SB 207499	193	132.6	16.5	95	199	193	-3.5	15.7	-40	44
	VISIT 24/WEEK 84	PLACEBO	162	132.8	15.5	100	180	162	-1.4	14.7	-50	40
		SB 207499	336	132.2	15.7	98	192	336	-1.8	17.0	-65	53
	VISIT 25/WEEK 88	PLACEBO	53	132.3	18.2	90	170	53	-4.4	14.5	-35	30
		SB 207499	97	131.9	17.5	90	177	97	-1.9	17.6	-44	50
	VISIT 26/WEEK 92	PLACEBO	52	130.5	17.3	90	170	52	-6.0	14.2	-48	22
		SB 207499	95	132.4	18.7	90	180	95	-1.5	17.7	-42	38
	VISIT 27/WEEK 96	PLACEBO	160	132.4	17.6	80	180	160	-1.7	16.3	-50	62
		SB 207499	332	132.8	16.1	83	180	332	-1.2	15.3	-55	44
	VISIT 28/WEEK 100	PLACEBO	22	131.5	17.6	100	170	22	-6.5	17.7	-50	30
		SB 207499	49	134.5	19.8	80	190	49	3.9	17.3	-40	41
	VISIT 29/WEEK 104	PLACEBO	18	136.1	15.3	100	160	18	-1.7	14.6	-35	20
		SB 207499	40	136.5	19.6	95	180	40	4.5	19.0	-40	50

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.16

DESCRIPTIVE STATISTICS FOR STANDARD VITAL SIGNS BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Systolic BP (MM HG)	VISIT 30/WEEK 108	PLACEBO	130	134.3	15.7	90	180	130	0.7	15.4	-40	40
		SB 207499	276	134.4	16.4	89	180	276	-0.3	15.5	-41	41
	VISIT 31/WEEK 112	PLACEBO	9	137.8	18.6	120	180	9	-3.9	14.5	-20	20
		SB 207499	18	131.8	18.0	100	170	18	0.7	18.2	-30	40
	VISIT 32/WEEK 116	PLACEBO	9	135.0	18.0	110	160	9	-6.7	21.1	-40	20
		SB 207499	16	134.7	16.1	110	170	16	3.5	16.5	-25	20
	VISIT 33/WEEK 120	PLACEBO	91	132.7	14.9	100	165	91	-2.2	14.5	-52	42
		SB 207499	191	136.0	16.7	100	194	191	0.1	17.8	-55	47
	VISIT 34/WEEK 124	PLACEBO	3	133.3	5.8	130	140	3	-13.3	5.8	-20	-10
		SB 207499	3	133.3	15.3	120	150	3	-10.0	10.0	-20	0
Diastolic BP (MM HG)	VISIT 35/WEEK 128	PLACEBO	3	136.7	25.2	110	160	3	-10.0	20.0	-30	10
		SB 207499	3	140.0	17.3	120	150	3	-3.3	15.3	-20	10
	VISIT 36/WEEK 132	PLACEBO	36	131.8	14.3	100	160	36	-0.5	14.5	-35	25
		SB 207499	57	137.1	15.8	110	180	57	1.5	17.3	-40	35
	VISIT 37/WEEK 136	PLACEBO	1	100.0	.	100	100	1	-40.0	.	-40	-40
		SB 207499	2	130.0	14.1	120	140	2	0.0	0.0	0	0
	ENDPOINT	PLACEBO	240	133.8	16.7	90	184	240	-1.5	15.9	-50	45
		SB 207499	473	132.9	15.9	83	194	473	-1.4	17.3	-75	50
	BASELINE	PLACEBO	243	79.1	9.7	60	110	0	.	.	.	.
		SB 207499	480	79.1	9.6	50	119	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	242	77.7	10.0	50	105	242	-1.5	9.0	-25	25
		SB 207499	479	77.9	9.3	54	108	479	-1.2	8.6	-31	30
	VISIT 2/WEEK 1	PLACEBO	237	78.2	9.6	55	102	237	-1.0	9.1	-28	23
		SB 207499	466	77.5	10.4	50	120	466	-1.6	10.3	-43	35
	VISIT 3/WEEK 2	PLACEBO	228	78.3	10.4	50	118	228	-0.9	9.6	-34	26
		SB 207499	460	77.7	9.4	50	124	460	-1.4	9.6	-39	32
	VISIT 4/WEEK 4	PLACEBO	219	78.3	10.2	50	108	219	-0.9	9.6	-30	30
		SB 207499	459	77.7	9.6	50	118	459	-1.4	9.1	-36	20
	VISIT 5/WEEK 8	PLACEBO	213	78.3	10.2	50	109	213	-0.9	9.6	-25	30
		SB 207499	451	77.6	9.9	45	111	451	-1.6	9.4	-30	32

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.16

DESCRIPTIVE STATISTICS FOR STANDARD VITAL SIGNS BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	RESULT					CHANGE FROM BASELINE				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Diastolic BP (MM HG)	VISIT 6/WEEK 12	PLACEBO	207	77.7	10.3	40	108	207	-1.5	9.3	-30	20
		SB 207499	443	78.1	10.2	40	120	443	-1.2	9.7	-37	28
	VISIT 7/WEEK 16	PLACEBO	202	78.4	9.9	54	110	202	-0.5	8.8	-25	26
		SB 207499	438	78.0	9.8	50	114	438	-1.3	9.6	-31	31
	VISIT 8/WEEK 20	PLACEBO	197	77.9	9.7	50	106	197	-1.1	9.1	-30	25
		SB 207499	434	77.2	9.7	50	117	434	-2.1	8.9	-36	26
	VISIT 9/WEEK 24	PLACEBO	193	78.5	9.4	50	110	193	-0.4	8.5	-30	30
		SB 207499	428	77.9	10.2	50	120	428	-1.4	9.1	-30	30
	VISIT 10/WEEK 28	PLACEBO	191	78.4	9.7	60	114	191	-0.5	9.5	-30	30
		SB 207499	422	77.7	9.9	50	115	422	-1.5	9.2	-30	30
	VISIT 11/WEEK 32	PLACEBO	187	78.1	9.5	50	101	187	-0.8	9.0	-28	30
		SB 207499	419	78.3	9.8	60	120	419	-1.0	9.4	-30	32
	VISIT 12/WEEK 36	PLACEBO	187	77.7	9.5	50	101	187	-1.1	8.7	-25	29
		SB 207499	413	77.8	10.4	50	112	413	-1.5	9.2	-30	32
	VISIT 13/WEEK 40	PLACEBO	184	78.2	9.4	50	100	184	-0.7	9.9	-30	35
		SB 207499	407	77.3	9.8	49	115	407	-1.8	9.2	-40	35
	VISIT 14/WEEK 44	PLACEBO	184	76.6	8.8	60	100	184	-2.2	8.7	-20	23
		SB 207499	405	76.9	9.6	50	123	405	-2.2	9.4	-35	45
	VISIT 15/WEEK 48	PLACEBO	184	77.7	8.6	60	100	184	-1.1	8.9	-20	20
		SB 207499	402	77.6	9.8	50	111	402	-1.6	8.6	-30	26
VISIT 16/WEEK 52	PLACEBO	180	77.7	9.2	55	105	180	-1.2	9.4	-25	25	
	SB 207499	386	77.3	9.3	50	110	386	-2.2	8.9	-36	20	
VISIT 17/WEEK 56	PLACEBO	172	76.9	9.4	55	110	172	-1.9	8.8	-20	28	
	SB 207499	367	78.3	10.0	50	114	367	-1.1	9.9	-35	26	
VISIT 18/WEEK 60	PLACEBO	174	77.0	9.5	50	100	174	-1.7	9.8	-25	34	
	SB 207499	374	77.2	10.3	47	113	374	-2.0	9.7	-34	25	
VISIT 19/WEEK 64	PLACEBO	142	78.3	9.4	60	100	142	-0.9	9.1	-20	30	
	SB 207499	311	78.7	10.6	50	127	311	-1.2	9.7	-35	35	
VISIT 20/WEEK 68	PLACEBO	140	77.5	9.7	50	105	140	-1.6	9.9	-25	30	
	SB 207499	299	78.9	10.6	56	123	299	-0.9	9.4	-25	31	

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

SB 207499

TABLE 15.16

DESCRIPTIVE STATISTICS FOR STANDARD VITAL SIGNS BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Diastolic BP (MM HG)	VISIT 21/WEEK 72	PLACEBO	171	77.4	9.3	60	111	171	-1.4	8.9	-20	20
		SB 207499	359	78.4	10.5	48	120	359	-0.7	10.0	-38	40
	VISIT 22/WEEK 76	PLACEBO	100	77.7	10.2	50	105	100	-1.0	9.4	-25	20
		SB 207499	199	77.0	10.1	50	110	199	-2.4	9.4	-30	20
	VISIT 23/WEEK 80	PLACEBO	98	76.9	10.8	45	111	98	-1.9	9.4	-30	28
		SB 207499	193	76.7	10.0	50	107	193	-2.6	9.6	-30	20
	VISIT 24/WEEK 84	PLACEBO	162	77.9	9.8	60	110	162	-0.7	9.9	-30	25
		SB 207499	336	77.1	10.2	50	135	336	-2.2	9.6	-30	57
	VISIT 25/WEEK 88	PLACEBO	53	75.8	9.8	45	95	53	-3.8	9.9	-30	20
		SB 207499	97	74.9	10.1	50	100	97	-4.2	10.8	-28	20
	VISIT 26/WEEK 92	PLACEBO	52	75.5	10.2	55	95	52	-4.0	9.7	-25	20
		SB 207499	95	75.5	10.5	58	105	95	-3.6	8.5	-21	18
	VISIT 27/WEEK 96	PLACEBO	160	77.6	9.9	54	115	160	-1.1	10.0	-25	34
		SB 207499	332	77.6	9.9	50	107	332	-1.8	9.2	-30	25
	VISIT 28/WEEK 100	PLACEBO	22	77.3	9.2	60	90	22	-0.9	10.3	-25	20
		SB 207499	49	75.7	10.6	60	110	49	-0.7	8.3	-20	20
	VISIT 29/WEEK 104	PLACEBO	18	73.6	8.9	60	90	18	-4.4	10.0	-20	10
		SB 207499	40	73.5	10.7	55	100	40	-2.7	9.1	-20	13
	VISIT 30/WEEK 108	PLACEBO	130	78.3	9.7	50	120	130	0.0	10.4	-26	26
		SB 207499	276	78.1	10.7	50	122	276	-1.2	9.9	-36	30
	VISIT 31/WEEK 112	PLACEBO	9	78.3	10.6	60	100	9	-1.7	7.5	-10	10
		SB 207499	18	75.9	12.4	60	100	18	-1.9	9.1	-20	15
	VISIT 32/WEEK 116	PLACEBO	9	76.7	8.7	60	90	9	-3.3	11.5	-25	10
		SB 207499	16	76.2	13.3	60	110	16	-1.4	10.7	-20	20
	VISIT 33/WEEK 120	PLACEBO	91	77.7	8.0	60	100	91	-1.1	8.3	-20	24
		SB 207499	191	79.2	9.2	60	115	191	-0.6	9.4	-30	32
	VISIT 34/WEEK 124	PLACEBO	3	76.7	5.8	70	80	3	-1.7	12.6	-15	10
		SB 207499	3	81.7	2.9	80	85	3	3.3	5.8	0	10
	VISIT 35/WEEK 128	PLACEBO	3	75.0	8.7	70	85	3	-3.3	16.1	-15	15
		SB 207499	3	86.7	5.8	80	90	3	8.3	2.9	5	10

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.16

DESCRIPTIVE STATISTICS FOR STANDARD VITAL SIGNS BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Diastolic BP (MM HG)	VISIT 36/WEEK 132	PLACEBO	36	76.7	10.3	45	92	36	-2.2	11.7	-35	30
		SB 207499	57	78.3	9.9	60	110	57	-2.3	10.8	-22	20
	VISIT 37/WEEK 136	PLACEBO	1	70.0	.	70	70	1	-10.0	.	-10	-10
		SB 207499	2	85.0	7.1	80	90	2	7.5	3.5	5	10
Heart Rate (BPM)	ENDPOINT	PLACEBO	240	78.3	8.9	60	108	240	-0.8	9.4	-21	30
		SB 207499	473	77.4	10.0	50	115	473	-1.7	9.9	-30	32
	BASELINE	PLACEBO	243	76.8	9.6	58	106	0	.	.	.	.
		SB 207499	480	76.3	10.7	48	109	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	242	76.7	10.6	51	111	242	-0.0	9.5	-38	33
		SB 207499	478	76.8	11.6	49	136	478	0.5	10.2	-30	39
	VISIT 2/WEEK 1	PLACEBO	238	76.2	11.0	50	114	238	-0.9	10.5	-32	38
		SB 207499	467	76.3	10.7	47	109	467	0.2	10.3	-30	37
	VISIT 3/WEEK 2	PLACEBO	228	75.8	11.2	48	113	228	-1.4	10.6	-36	32
		SB 207499	460	76.1	11.2	49	126	460	-0.1	10.8	-36	34
	VISIT 4/WEEK 4	PLACEBO	219	76.1	10.4	50	110	219	-0.9	10.4	-40	28
		SB 207499	459	75.9	10.8	54	110	459	-0.5	10.5	-37	46
	VISIT 5/WEEK 8	PLACEBO	213	76.1	11.0	53	104	213	-1.0	11.4	-40	32
		SB 207499	450	76.1	11.6	43	120	450	-0.2	11.4	-36	60
	VISIT 6/WEEK 12	PLACEBO	207	76.7	12.3	50	118	207	-0.2	12.1	-27	36
		SB 207499	443	76.1	11.6	41	123	443	-0.2	10.4	-46	48
	VISIT 7/WEEK 16	PLACEBO	202	76.2	11.8	51	116	202	-0.9	11.1	-40	32
		SB 207499	438	76.7	11.4	42	121	438	0.3	10.9	-36	37
	VISIT 8/WEEK 20	PLACEBO	197	77.5	11.9	52	112	197	0.6	11.4	-32	34
		SB 207499	433	76.9	11.9	40	128	433	0.6	11.2	-32	50
	VISIT 9/WEEK 24	PLACEBO	193	77.0	11.5	55	110	193	0.0	11.2	-40	34
		SB 207499	428	76.0	12.0	39	127	428	-0.3	11.4	-40	48
	VISIT 10/WEEK 28	PLACEBO	191	77.4	11.3	52	106	191	0.5	11.2	-40	32
		SB 207499	422	76.0	11.6	45	129	422	-0.4	10.8	-32	35
	VISIT 11/WEEK 32	PLACEBO	187	76.8	11.0	40	108	187	0.1	10.7	-40	32
		SB 207499	419	75.9	11.9	34	115	419	-0.5	10.6	-35	32

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.16

DESCRIPTIVE STATISTICS FOR STANDARD VITAL SIGNS BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Heart Rate (BPM)	VISIT 12/WEEK 36	PLACEBO	187	76.4	11.7	50	116	187	-0.3	11.4	-38	40
		SB 207499	413	76.0	11.6	48	130	413	-0.5	10.3	-36	38
	VISIT 13/WEEK 40	PLACEBO	182	75.9	11.6	50	110	182	-0.7	11.6	-36	40
		SB 207499	407	76.1	11.4	39	115	407	-0.3	10.6	-30	43
	VISIT 14/WEEK 44	PLACEBO	184	77.4	12.5	48	133	184	0.6	13.3	-42	61
		SB 207499	405	76.1	11.7	37	130	405	-0.5	11.1	-39	62
	VISIT 15/WEEK 48	PLACEBO	184	77.0	12.2	44	120	184	0.1	11.7	-40	52
		SB 207499	402	75.7	11.6	45	132	402	-0.8	10.7	-40	46
	VISIT 16/WEEK 52	PLACEBO	180	76.5	11.3	50	114	180	-0.3	11.4	-40	36
		SB 207499	386	76.0	11.1	51	120	386	-0.5	11.1	-32	36
	VISIT 17/WEEK 56	PLACEBO	172	76.5	11.5	42	110	172	-0.6	11.3	-42	35
		SB 207499	367	76.5	11.7	48	123	367	-0.2	11.3	-42	48
	VISIT 18/WEEK 60	PLACEBO	174	77.0	13.4	44	130	174	-0.1	13.0	-40	40
		SB 207499	374	77.3	12.5	39	138	374	0.7	10.4	-30	38
	VISIT 19/WEEK 64	PLACEBO	141	77.0	12.0	40	108	141	0.2	12.3	-44	37
		SB 207499	311	76.5	11.3	53	131	311	-0.8	11.1	-36	40
	VISIT 20/WEEK 68	PLACEBO	140	76.6	12.8	40	110	140	-0.2	12.5	-44	41
		SB 207499	299	77.3	11.8	50	123	299	-0.1	10.7	-42	29
	VISIT 21/WEEK 72	PLACEBO	171	77.5	11.5	44	118	171	0.4	10.9	-40	38
		SB 207499	359	76.3	11.7	38	133	359	-0.2	11.4	-28	33
	VISIT 22/WEEK 76	PLACEBO	99	78.5	13.4	51	120	99	1.4	12.4	-37	36
		SB 207499	199	77.9	12.3	52	130	199	0.5	12.0	-34	62
	VISIT 23/WEEK 80	PLACEBO	98	77.9	12.0	46	110	98	1.0	11.0	-33	32
		SB 207499	193	76.8	10.8	50	127	193	-0.8	11.6	-34	59
	VISIT 24/WEEK 84	PLACEBO	162	77.3	13.0	44	120	162	0.2	12.8	-34	40
		SB 207499	336	75.3	11.7	45	133	336	-1.3	11.0	-37	50
	VISIT 25/WEEK 88	PLACEBO	53	78.6	13.0	56	108	53	1.2	14.2	-32	30
		SB 207499	97	75.2	11.2	49	101	97	-3.3	10.1	-27	28
	VISIT 26/WEEK 92	PLACEBO	52	76.9	13.1	52	108	52	-0.3	12.8	-36	24
		SB 207499	95	76.1	13.0	52	130	95	-2.5	13.2	-33	62

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.16

DESCRIPTIVE STATISTICS FOR STANDARD VITAL SIGNS BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Heart Rate (BPM)	VISIT 27/WEEK 96	PLACEBO	160	77.4	11.8	55	110	160	0.4	11.7	-32	40
		SB 207499	332	77.0	11.8	50	136	332	0.4	11.7	-38	52
	VISIT 28/WEEK 100	PLACEBO	22	74.5	13.0	56	100	22	-5.3	12.4	-40	10
		SB 207499	49	76.7	14.0	51	134	49	-3.3	15.5	-33	66
	VISIT 29/WEEK 104	PLACEBO	18	74.0	14.8	48	110	18	-6.3	14.3	-40	20
		SB 207499	40	76.6	14.2	52	125	40	-4.4	16.4	-33	57
	VISIT 30/WEEK 108	PLACEBO	130	77.3	12.0	49	112	130	0.4	11.9	-36	39
		SB 207499	276	76.3	11.7	50	120	276	-0.3	12.1	-38	52
	VISIT 31/WEEK 112	PLACEBO	9	66.4	7.7	54	77	9	-11.3	12.5	-32	5
		SB 207499	18	81.4	12.1	58	100	18	-3.7	15.0	-26	32
	VISIT 32/WEEK 116	PLACEBO	9	67.6	7.7	60	77	9	-10.2	10.3	-24	5
		SB 207499	16	80.4	15.2	64	120	16	-2.4	18.6	-27	52
	VISIT 33/WEEK 120	PLACEBO	91	78.0	12.0	46	108	91	1.8	12.7	-38	39
		SB 207499	191	77.5	11.5	52	115	191	0.2	12.1	-43	40
	VISIT 34/WEEK 124	PLACEBO	3	60.0	16.0	44	76	3	-17.3	19.7	-40	-4
		SB 207499	3	87.7	10.6	78	99	3	8.7	3.8	6	13
	VISIT 35/WEEK 128	PLACEBO	3	69.3	23.0	46	92	3	-8.0	26.5	-38	12
		SB 207499	3	85.0	3.0	82	88	3	6.0	8.7	-4	12
	VISIT 36/WEEK 132	PLACEBO	36	77.2	14.2	48	112	36	1.6	12.9	-36	31
		SB 207499	57	78.9	10.9	55	110	57	1.3	13.0	-36	40
	VISIT 37/WEEK 136	PLACEBO	1	78.0	.	78	78	1	-2.0	.	-2	-2
		SB 207499	2	87.5	24.7	70	105	2	5.5	10.6	-2	13
	ENDPOINT	PLACEBO	240	78.5	11.9	48	112	240	1.6	12.2	-36	50
		SB 207499	473	77.2	12.2	46	123	473	1.1	12.5	-43	60

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.17

TRANSITIONS FROM BASELINE IN SITTING VITAL SIGNS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

		PARAMETER: SYSTOLIC BP	TIME POINT: TOTAL ON-THERAPY								
PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	LOW CONCERN	ON-THERAPY							
				LOW	NORMAL		HIGH		HIGH CONCERN		
PLACEBO	LOW CONCERN (<75 MM HG)	0	0	0	0	0	0		0		
	LOW (75-89 MM HG)	0	0	0	0	0	0		0		
	NORMAL (90-139 MM HG)	133	0	1 (0.8%)	45 (33.8%)	86 (64.7%)	1 (0.8%)				
	HIGH (140-180 MM HG)	105	0	1 (1.0%)	7 (6.7%)	92 (87.6%)	6 (5.7%)				
	HIGH CONCERN (>180 MM HG)	2	0	0	0	2 (100.0%)	0				
	TOTAL	240	0	2 (0.8%)	52 (21.7%)	180 (75.0%)	7 (2.9%)				
SB 207499	LOW CONCERN (<75 MM HG)	0	0	0	0	0	0		0		
	LOW (75-89 MM HG)	0	0	0	0	0	0		0		
	NORMAL (90-139 MM HG)	271	0	8 (3.0%)	73 (26.9%)	189 (69.7%)	3 (1.1%)				
	HIGH (140-180 MM HG)	195	0	0	9 (4.6%)	174 (89.2%)	12 (6.2%)				
	HIGH CONCERN (>180 MM HG)	7	0	0	0	3 (42.9%)	4 (57.1%)				
	TOTAL	473	0	8 (1.7%)	82 (17.3%)	366 (77.4%)	19 (4.0%)				
TOTAL	LOW CONCERN (<75 MM HG)	0	0	0	0	0	0		0		
	LOW (75-89 MM HG)	0	0	0	0	0	0		0		
	NORMAL (90-139 MM HG)	404	0	9 (2.2%)	118 (29.2%)	275 (68.1%)	4 (1.0%)				
	HIGH (140-180 MM HG)	300	0	1 (0.3%)	16 (5.3%)	266 (88.7%)	18 (6.0%)				
	HIGH CONCERN (>180 MM HG)	9	0	0	0	5 (55.6%)	4 (44.4%)				
	TOTAL	713	0	10 (1.4%)	134 (18.8%)	546 (76.6%)	26 (3.6%)				

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS SITTING VITAL SIGNS COLLECTED DURING EXTENSION PERIOD

TABLE 15.17

TRANSITIONS FROM BASELINE IN SITTING VITAL SIGNS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: SYSTOLIC BP TIME POINT: ENDPOINT

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----								
			LOW CONCERN	LOW	NORMAL		HIGH	HIGH CONCERN			
PLACEBO	LOW CONCERN (<75 MM HG)	0	0	0	0	0	0	0			
	LOW (75-89 MM HG)	0	0	0	0	0	0	0			
	NORMAL (90-139 MM HG)	133	0	0	104	(78.2%)	29	(21.8%)	0		
	HIGH (140-180 MM HG)	105	0	0	35	(33.3%)	69	(65.7%)	1	(1.0%)	
	HIGH CONCERN (>180 MM HG)	2	0	0	0		2	(100.0%)	0		
	TOTAL	240	0	0	139	(57.9%)	100	(41.7%)	1	(0.4%)	
SB 207499	LOW CONCERN (<75 MM HG)	0	0	0	0	0	0	0			
	LOW (75-89 MM HG)	0	0	0	0	0	0	0			
	NORMAL (90-139 MM HG)	271	0	1	(0.4%)	191	(70.5%)	78	(28.8%)	1	(0.4%)
	HIGH (140-180 MM HG)	195	0	0		88	(45.1%)	106	(54.4%)	1	(0.5%)
	HIGH CONCERN (>180 MM HG)	7	0	0		2	(28.6%)	5	(71.4%)	0	
	TOTAL	473	0	1	(0.2%)	281	(59.4%)	189	(40.0%)	2	(0.4%)
TOTAL	LOW CONCERN (<75 MM HG)	0	0	0	0	0	0	0			
	LOW (75-89 MM HG)	0	0	0	0	0	0	0			
	NORMAL (90-139 MM HG)	404	0	1	(0.2%)	295	(73.0%)	107	(26.5%)	1	(0.2%)
	HIGH (140-180 MM HG)	300	0	0		123	(41.0%)	175	(58.3%)	2	(0.7%)
	HIGH CONCERN (>180 MM HG)	9	0	0		2	(22.2%)	7	(77.8%)	0	
	TOTAL	713	0	1	(0.1%)	420	(58.9%)	289	(40.5%)	3	(0.4%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS SITTING VITAL SIGNS COLLECTED DURING EXTENSION PERIOD

SB 207499

TABLE 15.17

TRANSITIONS FROM BASELINE IN SITTING VITAL SIGNS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: DIASTOLIC BP TIME POINT: TOTAL ON-THERAPY

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN	
PLACEBO	LOW CONCERN (<50 MM HG)	0	0	0	0	0	0	0
	LOW (50-59 MM HG)	0	0	0	0	0	0	0
	NORMAL (60-89 MM HG)	200	3 (1.5%)	17 (8.5%)	105 (52.5%)	78 (39.0%)	1 (0.5%)	
	HIGH (90-110 MM HG)	40	0	0	6 (15.0%)	29 (72.5%)	5 (12.5%)	
	HIGH CONCERN (>110 MM HG)	0	0	0	0	0	0	
	TOTAL	240	3 (1.3%)	17 (7.1%)	111 (46.3%)	107 (44.6%)	6 (2.5%)	
SB 207499	LOW CONCERN (<50 MM HG)	0	0	0	0	0	0	0
	LOW (50-59 MM HG)	2	1 (50.0%)	1 (50.0%)	0	0	0	0
	NORMAL (60-89 MM HG)	394	2 (0.5%)	36 (9.1%)	180 (45.7%)	181 (45.9%)	2 (0.5%)	
	HIGH (90-110 MM HG)	76	0	0	10 (13.2%)	58 (76.3%)	8 (10.5%)	
	HIGH CONCERN (>110 MM HG)	1	0	0	0	0	1 (100.0%)	
	TOTAL	473	3 (0.6%)	37 (7.8%)	190 (40.2%)	239 (50.5%)	11 (2.3%)	
TOTAL	LOW CONCERN (<50 MM HG)	0	0	0	0	0	0	0
	LOW (50-59 MM HG)	2	1 (50.0%)	1 (50.0%)	0	0	0	0
	NORMAL (60-89 MM HG)	594	5 (0.8%)	53 (8.9%)	285 (48.0%)	259 (43.6%)	3 (0.5%)	
	HIGH (90-110 MM HG)	116	0	0	16 (13.8%)	87 (75.0%)	13 (11.2%)	
	HIGH CONCERN (>110 MM HG)	1	0	0	0	0	1 (100.0%)	
	TOTAL	713	6 (0.8%)	54 (7.6%)	301 (42.2%)	346 (48.5%)	17 (2.4%)	

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS SITTING VITAL SIGNS COLLECTED DURING EXTENSION PERIOD

TABLE 15.17

TRANSITIONS FROM BASELINE IN SITTING VITAL SIGNS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: DIASTOLIC BP TIME POINT: ENDPOINT

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<50 MM HG)	0	0	0	0	0	0
	LOW (50-59 MM HG)	0	0	0	0	0	0
	NORMAL (60-89 MM HG)	200	0	0	183 (91.5%)	17 (8.5%)	0
	HIGH (90-110 MM HG)	40	0	0	27 (67.5%)	13 (32.5%)	0
	HIGH CONCERN (>110 MM HG)	0	0	0	0	0	0
	TOTAL	240	0	0	210 (87.5%)	30 (12.5%)	0
SB 207499	LOW CONCERN (<50 MM HG)	0	0	0	0	0	0
	LOW (50-59 MM HG)	2	0	0	2 (100.0%)	0	0
	NORMAL (60-89 MM HG)	394	0	6 (1.5%)	348 (88.3%)	40 (10.2%)	0
	HIGH (90-110 MM HG)	76	0	0	50 (65.8%)	24 (31.6%)	2 (2.6%)
	HIGH CONCERN (>110 MM HG)	1	0	0	0	1 (100.0%)	0
	TOTAL	473	0	6 (1.3%)	400 (84.6%)	65 (13.7%)	2 (0.4%)
TOTAL	LOW CONCERN (<50 MM HG)	0	0	0	0	0	0
	LOW (50-59 MM HG)	2	0	0	2 (100.0%)	0	0
	NORMAL (60-89 MM HG)	594	0	6 (1.0%)	531 (89.4%)	57 (9.6%)	0
	HIGH (90-110 MM HG)	116	0	0	77 (66.4%)	37 (31.9%)	2 (1.7%)
	HIGH CONCERN (>110 MM HG)	1	0	0	0	1 (100.0%)	0
	TOTAL	713	0	6 (0.8%)	610 (85.6%)	95 (13.3%)	2 (0.3%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS SITTING VITAL SIGNS COLLECTED DURING EXTENSION PERIOD

SB 207499

TABLE 15.17

TRANSITIONS FROM BASELINE IN SITTING VITAL SIGNS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

		PARAMETER: HEART RATE		TIME POINT: TOTAL ON-THERAPY							
PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	LOW CONCERN		LOW		ON-THERAPY		HIGH		HIGH CONCERN
PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0		0
	LOW (50-59 BPM)	5	2 (40.0%)		1 (20.0%)		2 (40.0%)		0		0
	NORMAL (60-99 BPM)	230	3 (1.3%)		43 (18.7%)		130 (56.5%)		53 (23.0%)		3 (1.3%)
	HIGH (100-120 BPM)	5	0		1 (20.0%)		1 (20.0%)		4 (80.0%)		0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	240	5 (2.1%)		45 (18.8%)		133 (55.4%)		57 (23.8%)		3 (1.3%)
SB 207499	LOW CONCERN (<50 BPM)	1	0		0		1 (100.0%)		0		0
	LOW (50-59 BPM)	13	3 (23.1%)		9 (69.2%)		1 (7.7%)		0		0
	NORMAL (60-99 BPM)	443	11 (2.5%)		75 (16.9%)		276 (62.3%)		83 (18.7%)		5 (1.1%)
	HIGH (100-120 BPM)	16	0		1 (6.3%)		3 (18.8%)		10 (62.5%)		3 (18.8%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	473	14 (3.0%)		85 (18.0%)		281 (59.4%)		93 (19.7%)		8 (1.7%)
TOTAL	LOW CONCERN (<50 BPM)	1	0		0		1 (100.0%)		0		0
	LOW (50-59 BPM)	18	5 (27.8%)		10 (55.6%)		3 (16.7%)		0		0
	NORMAL (60-99 BPM)	673	14 (2.1%)		118 (17.5%)		406 (60.3%)		136 (20.2%)		8 (1.2%)
	HIGH (100-120 BPM)	21	0		2 (9.5%)		4 (19.0%)		14 (66.7%)		3 (14.3%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	713	19 (2.7%)		130 (18.2%)		414 (58.1%)		150 (21.0%)		11 (1.5%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS SITTING VITAL SIGNS COLLECTED DURING EXTENSION PERIOD

TABLE 15.17

TRANSITIONS FROM BASELINE IN SITTING VITAL SIGNS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: HEART RATE TIME POINT: ENDPOINT

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN			
PLACEBO	LOW CONCERN (<50 BPM)	0	0	0	0	0	0			
	LOW (50-59 BPM)	5	0	1 (20.0%)	4 (80.0%)	0	0			
	NORMAL (60-99 BPM)	230	1 (0.4%)	5 (2.2%)	208 (90.4%)	16 (7.0%)	0			
	HIGH (100-120 BPM)	5	0	0	3 (60.0%)	2 (40.0%)	0			
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0			
	TOTAL	240	1 (0.4%)	6 (2.5%)	215 (89.6%)	18 (7.5%)	0			
SB 207499	LOW CONCERN (<50 BPM)	1	0	0	1 (100.0%)	0	0			
	LOW (50-59 BPM)	13	1 (7.7%)	4 (30.8%)	8 (61.5%)	0	0			
	NORMAL (60-99 BPM)	443	0	13 (2.9%)	412 (93.0%)	17 (3.8%)	1 (0.2%)			
	HIGH (100-120 BPM)	16	0	0	11 (68.8%)	5 (31.3%)	0			
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0			
	TOTAL	473	1 (0.2%)	17 (3.6%)	432 (91.3%)	22 (4.7%)	1 (0.2%)			
TOTAL	LOW CONCERN (<50 BPM)	1	0	0	1 (100.0%)	0	0			
	LOW (50-59 BPM)	18	1 (5.6%)	5 (27.8%)	12 (66.7%)	0	0			
	NORMAL (60-99 BPM)	673	1 (0.1%)	18 (2.7%)	620 (92.1%)	33 (4.9%)	1 (0.1%)			
	HIGH (100-120 BPM)	21	0	0	14 (66.7%)	7 (33.3%)	0			
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0			
	TOTAL	713	2 (0.3%)	23 (3.2%)	647 (90.7%)	40 (5.6%)	1 (0.1%)			

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS SITTING VITAL SIGNS COLLECTED DURING EXTENSION PERIOD

TABLE 15.18

DESCRIPTIVE STATISTICS FOR ECGS BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Atrial Rate (BPM)	BASELINE	PLACEBO	243	74.0	12.2	50	111	0	.	.	.	.
		SB 207499	478	74.1	12.8	41	109	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	243	76.2	20.8	48	322	243	2.3	18.1	-29	231
		SB 207499	480	75.4	12.8	40	116	478	1.3	10.7	-37	65
	VISIT 2/WEEK 1	PLACEBO	234	75.3	13.0	46	122	234	1.0	11.0	-37	41
		SB 207499	462	74.9	13.2	43	122	460	1.0	11.9	-40	56
	VISIT 3/WEEK 2	PLACEBO	223	74.3	12.7	50	113	223	0.0	11.2	-32	36
		SB 207499	451	75.3	16.8	44	300	450	1.3	16.6	-37	253
	VISIT 4/WEEK 4	PLACEBO	215	75.9	14.1	48	141	215	1.4	12.0	-33	54
		SB 207499	458	74.9	13.1	40	124	456	0.9	11.2	-42	53
	VISIT 5/WEEK 8	PLACEBO	213	75.8	13.4	51	125	213	1.3	11.4	-31	50
		SB 207499	447	74.8	13.5	43	123	445	0.9	11.7	-44	58
	VISIT 6/WEEK 12	PLACEBO	208	75.7	13.8	47	118	208	1.3	12.4	-31	49
		SB 207499	444	74.6	13.1	40	117	442	0.6	10.9	-45	52
	VISIT 7/WEEK 16	PLACEBO	202	75.6	13.3	45	112	202	1.1	11.1	-37	41
		SB 207499	436	76.4	19.0	46	274	434	2.2	17.8	-45	219
	VISIT 8/WEEK 20	PLACEBO	197	76.7	13.9	45	120	197	2.3	12.6	-43	47
		SB 207499	431	76.1	16.4	44	275	430	2.0	15.2	-50	222
	VISIT 9/WEEK 24	PLACEBO	193	77.7	23.3	48	335	193	3.1	23.2	-36	270
		SB 207499	427	75.7	16.7	43	272	425	1.4	15.7	-39	219
	VISIT 10/WEEK 28	PLACEBO	190	76.7	14.0	46	130	190	2.2	11.6	-28	43
		SB 207499	422	75.8	16.3	36	282	420	1.5	15.9	-38	229
	VISIT 11/WEEK 32	PLACEBO	186	75.8	13.3	48	117	186	1.3	12.1	-29	54
		SB 207499	419	76.0	16.4	41	268	417	1.8	15.4	-31	215
	VISIT 12/WEEK 36	PLACEBO	187	75.6	14.5	50	146	187	1.1	13.0	-38	59
		SB 207499	410	75.7	16.9	40	293	408	1.6	16.7	-42	240
	VISIT 13/WEEK 40	PLACEBO	185	75.4	12.8	48	111	185	0.9	11.4	-30	48
		SB 207499	404	75.6	15.7	41	252	402	1.4	15.4	-43	199
	VISIT 14/WEEK 44	PLACEBO	183	76.7	14.5	41	133	183	2.0	14.3	-36	74
		SB 207499	404	76.7	19.1	41	270	402	2.5	19.1	-49	217

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.18

DESCRIPTIVE STATISTICS FOR ECGS BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Atrial Rate (BPM)	VISIT 15/WEEK 48	PLACEBO	184	76.3	14.8	40	127	184	1.7	13.1	-37	58
		SB 207499	398	74.8	13.4	39	122	396	0.6	11.4	-33	57
	VISIT 16/WEEK 52	PLACEBO	180	76.9	16.6	43	201	180	2.4	15.3	-38	123
		SB 207499	384	75.2	12.6	41	112	382	0.9	11.6	-44	37
	VISIT 17/WEEK 56	PLACEBO	169	76.5	13.4	45	114	169	2.2	11.1	-33	46
		SB 207499	364	76.7	16.8	43	265	362	2.3	16.4	-37	199
	VISIT 18/WEEK 60	PLACEBO	173	76.2	14.7	45	130	173	1.6	12.7	-39	42
		SB 207499	374	77.5	18.8	43	269	372	3.2	18.8	-35	203
	VISIT 19/WEEK 64	PLACEBO	142	76.0	13.6	45	109	142	1.8	12.2	-43	38
		SB 207499	308	78.1	22.3	43	278	306	2.8	21.4	-34	208
	VISIT 20/WEEK 68	PLACEBO	140	76.1	13.3	43	113	140	1.8	11.3	-29	30
		SB 207499	295	76.1	13.0	41	127	293	0.8	10.8	-36	34
	VISIT 21/WEEK 72	PLACEBO	170	75.9	13.6	43	120	170	1.2	11.6	-33	60
		SB 207499	357	76.3	18.2	38	266	355	2.1	17.9	-34	213
	VISIT 22/WEEK 76	PLACEBO	100	77.2	15.9	51	123	100	2.1	15.5	-41	55
		SB 207499	198	77.7	18.6	51	259	196	2.9	17.9	-28	193
	VISIT 23/WEEK 80	PLACEBO	98	76.7	14.8	46	107	98	1.6	12.6	-30	37
		SB 207499	193	76.9	19.0	47	272	191	2.3	18.4	-32	206
	VISIT 24/WEEK 84	PLACEBO	163	76.0	14.3	49	119	163	1.5	12.9	-44	47
		SB 207499	334	74.9	13.5	44	135	332	0.8	11.7	-48	69
	VISIT 25/WEEK 88	PLACEBO	53	76.1	14.0	53	106	53	0.3	13.2	-41	32
		SB 207499	97	76.8	23.8	46	268	97	2.6	23.2	-30	202
	VISIT 26/WEEK 92	PLACEBO	52	75.2	14.6	43	107	52	-0.6	12.9	-40	21
		SB 207499	96	77.8	25.5	41	281	96	3.4	24.6	-32	215
	VISIT 27/WEEK 96	PLACEBO	160	75.7	13.9	43	114	160	1.3	12.3	-35	41
		SB 207499	328	77.7	25.7	46	379	326	3.8	25.6	-34	307
	VISIT 28/WEEK 100	PLACEBO	22	75.2	15.0	54	112	22	-2.0	12.2	-44	20
		SB 207499	49	78.5	29.6	51	261	48	3.8	30.0	-31	195
	VISIT 29/WEEK 104	PLACEBO	18	73.5	16.2	53	111	18	-4.1	14.4	-43	12
		SB 207499	39	76.6	13.9	52	108	39	0.5	11.1	-30	27

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.18

DESCRIPTIVE STATISTICS FOR ECGS BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Atrial Rate (BPM)	VISIT 30/WEEK 108	PLACEBO	126	76.7	14.9	45	123	126	2.1	13.1	-37	36
		SB 207499	272	75.4	13.7	45	130	271	0.8	12.0	-38	64
	VISIT 31/WEEK 112	PLACEBO	9	65.4	7.9	51	77	9	-6.9	14.6	-40	9
		SB 207499	18	78.3	12.8	51	97	18	-1.8	12.1	-34	17
	VISIT 32/WEEK 116	PLACEBO	9	66.0	7.4	57	77	9	-6.3	15.4	-41	9
		SB 207499	16	89.6	44.8	53	250	16	10.9	47.3	-17	184
	VISIT 33/WEEK 120	PLACEBO	91	76.1	13.8	45	109	91	2.1	13.5	-37	45
		SB 207499	187	77.0	14.1	48	120	187	1.8	12.2	-43	39
	VISIT 34/WEEK 124	PLACEBO	3	69.0	12.1	56	80	3	-3.0	6.2	-8	4
		SB 207499	3	83.7	15.5	68	99	3	7.3	9.0	-3	13
Ventricular Rate (BPM)	VISIT 35/WEEK 128	PLACEBO	3	79.3	10.6	68	89	3	7.3	5.5	2	13
		SB 207499	3	83.7	10.1	73	93	3	7.3	5.5	2	13
	VISIT 36/WEEK 132	PLACEBO	36	75.1	13.9	49	108	36	1.0	14.0	-32	27
		SB 207499	58	79.2	15.6	35	116	58	2.6	13.2	-18	48
	VISIT 37/WEEK 136	PLACEBO	1	77.0	.	77	77	1	1.0	.	1	1
		SB 207499	2	84.0	24.0	67	101	2	5.5	13.4	-4	15
	ENDPOINT	PLACEBO	239	77.2	14.1	45	127	239	3.1	12.9	-32	69
		SB 207499	471	76.7	14.3	35	127	469	2.8	13.3	-43	57
	BASELINE	PLACEBO	243	74.0	12.3	50	111	0	.	.	.	.
		SB 207499	480	74.1	12.8	41	109	0	.	.	.	.
Ventricular Rate (BPM)	VISIT 1/DAY 1	PLACEBO	243	75.3	13.5	48	131	243	1.3	10.6	-29	44
		SB 207499	480	75.4	12.8	40	116	480	1.3	10.7	-37	65
	VISIT 2/WEEK 1	PLACEBO	234	75.3	13.0	46	122	234	1.0	11.0	-37	41
		SB 207499	462	74.9	13.2	43	122	462	1.0	11.9	-40	56
	VISIT 3/WEEK 2	PLACEBO	223	74.3	12.7	50	113	223	-0.0	11.3	-32	36
		SB 207499	452	74.9	13.1	44	123	452	0.9	11.9	-37	72
Ventricular Rate (BPM)	VISIT 4/WEEK 4	PLACEBO	215	75.9	14.1	48	141	215	1.3	12.0	-33	54
		SB 207499	458	74.9	13.1	40	124	458	0.9	11.3	-42	53
Ventricular Rate (BPM)	VISIT 5/WEEK 8	PLACEBO	213	75.7	13.2	51	125	213	1.1	11.4	-31	50
		SB 207499	447	74.8	13.5	43	123	447	0.9	11.7	-44	58

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.18

DESCRIPTIVE STATISTICS FOR ECGS BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Ventricular Rate (BPM)	VISIT 6/WEEK 12	PLACEBO	208	75.7	13.8	47	118	208	1.2	12.3	-31	49
		SB 207499	444	74.6	13.1	40	117	444	0.6	11.0	-45	52
	VISIT 7/WEEK 16	PLACEBO	202	75.6	13.3	45	112	202	1.0	11.1	-37	41
		SB 207499	436	75.4	13.6	37	122	436	1.3	11.6	-45	70
	VISIT 8/WEEK 20	PLACEBO	197	76.7	13.9	45	120	197	2.2	12.7	-43	47
		SB 207499	432	75.6	13.5	35	119	432	1.5	10.9	-50	48
	VISIT 9/WEEK 24	PLACEBO	193	76.4	14.0	48	148	193	1.6	12.8	-36	61
		SB 207499	427	75.1	13.8	36	122	427	0.9	11.8	-39	51
	VISIT 10/WEEK 28	PLACEBO	190	76.7	14.0	46	130	190	2.1	11.6	-28	43
		SB 207499	422	75.1	12.8	36	127	422	0.9	11.3	-38	40
	VISIT 11/WEEK 32	PLACEBO	186	75.8	13.3	48	117	186	1.2	12.0	-29	54
		SB 207499	419	75.5	13.6	35	121	419	1.3	11.4	-31	54
	VISIT 12/WEEK 36	PLACEBO	187	75.6	14.5	50	146	187	1.0	12.9	-38	59
		SB 207499	410	75.1	13.1	40	121	410	1.0	11.8	-42	41
	VISIT 13/WEEK 40	PLACEBO	185	75.4	12.8	48	111	185	0.8	11.3	-30	48
		SB 207499	405	75.0	13.1	41	120	405	0.8	11.8	-43	56
	VISIT 14/WEEK 44	PLACEBO	183	76.7	14.5	41	133	183	2.0	14.2	-36	74
		SB 207499	404	75.7	13.6	37	139	404	1.6	12.4	-49	84
	VISIT 15/WEEK 48	PLACEBO	184	76.3	14.8	40	127	184	1.6	13.0	-37	58
		SB 207499	398	74.8	13.4	39	122	398	0.6	11.4	-33	57
	VISIT 16/WEEK 52	PLACEBO	180	76.2	13.7	43	117	180	1.7	12.3	-38	54
		SB 207499	384	75.2	12.6	41	112	384	0.9	11.6	-44	37
	VISIT 17/WEEK 56	PLACEBO	169	76.5	13.4	45	114	169	2.1	11.1	-33	46
		SB 207499	364	76.3	13.9	43	130	364	2.0	13.1	-37	72
	VISIT 18/WEEK 60	PLACEBO	173	76.2	14.7	45	130	173	1.6	12.7	-39	42
		SB 207499	374	76.5	13.5	40	121	374	2.3	12.2	-35	66
	VISIT 19/WEEK 64	PLACEBO	142	76.0	13.6	45	109	142	1.7	12.2	-43	38
		SB 207499	308	76.5	13.5	43	115	308	1.3	11.9	-34	56
	VISIT 20/WEEK 68	PLACEBO	140	76.1	13.3	43	113	140	1.7	11.3	-29	30
		SB 207499	295	76.1	13.0	41	127	295	0.9	10.8	-36	34

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.18

DESCRIPTIVE STATISTICS FOR ECGS BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Ventricular Rate (BPM)	VISIT 21/WEEK 72	PLACEBO	170	75.9	13.6	43	120	170	1.2	11.6	-33	60
		SB 207499	357	75.2	13.4	35	127	357	1.1	11.8	-34	42
	VISIT 22/WEEK 76	PLACEBO	100	77.2	15.9	51	123	100	1.9	15.2	-41	55
		SB 207499	198	76.9	13.5	51	118	198	2.1	11.8	-28	71
	VISIT 23/WEEK 80	PLACEBO	98	76.7	14.8	46	107	98	1.5	12.6	-30	37
		SB 207499	193	76.1	13.0	47	118	193	1.5	11.6	-32	52
	VISIT 24/WEEK 84	PLACEBO	163	76.0	14.3	49	119	163	1.4	12.9	-44	47
		SB 207499	334	74.9	13.5	44	135	334	0.8	11.7	-48	69
	VISIT 25/WEEK 88	PLACEBO	53	76.1	14.0	53	106	53	0.3	13.2	-41	32
		SB 207499	97	75.1	13.8	46	107	97	0.9	11.7	-30	41
	VISIT 26/WEEK 92	PLACEBO	52	75.2	14.6	43	107	52	-0.6	12.9	-40	21
		SB 207499	96	75.9	14.8	41	115	96	1.6	11.9	-32	37
	VISIT 27/WEEK 96	PLACEBO	160	75.7	13.9	43	114	160	1.2	12.5	-35	41
		SB 207499	328	75.8	13.6	46	123	328	1.8	12.1	-34	53
	VISIT 28/WEEK 100	PLACEBO	22	75.2	15.0	54	112	22	-2.5	12.3	-44	20
		SB 207499	49	75.4	13.7	51	108	49	0.6	11.9	-31	42
	VISIT 29/WEEK 104	PLACEBO	18	73.5	16.2	53	111	18	-4.1	14.4	-43	12
		SB 207499	40	77.4	14.6	52	108	40	1.6	12.8	-30	42
	VISIT 30/WEEK 108	PLACEBO	126	76.7	14.9	45	123	126	2.0	13.2	-37	36
		SB 207499	272	75.4	13.7	45	130	272	0.8	12.0	-38	64
	VISIT 31/WEEK 112	PLACEBO	9	65.4	7.9	51	77	9	-6.9	14.6	-40	9
		SB 207499	18	78.3	12.8	51	97	18	-1.8	12.1	-34	17
	VISIT 32/WEEK 116	PLACEBO	9	66.0	7.4	57	77	9	-6.3	15.4	-41	9
		SB 207499	16	80.0	14.1	53	106	16	1.3	13.0	-17	30
	VISIT 33/WEEK 120	PLACEBO	91	76.1	13.8	45	109	91	2.0	13.7	-37	45
		SB 207499	187	77.0	14.1	48	120	187	1.8	12.2	-43	39
	VISIT 34/WEEK 124	PLACEBO	3	69.0	12.1	56	80	3	-3.0	6.2	-8	4
		SB 207499	3	83.7	15.5	68	99	3	7.3	9.0	-3	13
	VISIT 35/WEEK 128	PLACEBO	3	79.3	10.6	68	89	3	7.3	5.5	2	13
		SB 207499	3	83.7	10.1	73	93	3	7.3	5.5	2	13

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.18

DESCRIPTIVE STATISTICS FOR ECGS BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Ventricular Rate (BPM)	VISIT 36/WEEK 132	PLACEBO	36	75.1	13.9	49	108	36	1.0	14.0	-32	27
		SB 207499	58	79.2	15.6	35	116	58	2.6	13.2	-18	48
	VISIT 37/WEEK 136	PLACEBO	1	77.0	.	77	77	1	1.0	.	1	1
		SB 207499	2	84.0	24.0	67	101	2	5.5	13.4	-4	15
	ENDPOINT	PLACEBO	239	77.2	14.1	45	127	239	3.0	13.0	-32	69
		SB 207499	471	76.7	14.3	35	127	471	2.8	13.3	-43	57
PR (MSEC)	BASELINE	PLACEBO	238	156.1	23.5	96	320	0	.	.	.	.
		SB 207499	471	158.8	25.8	104	383	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	236	156.7	24.7	104	332	234	0.4	14.5	-56	56
		SB 207499	468	159.2	26.3	96	360	466	0.5	13.5	-56	60
	VISIT 2/WEEK 1	PLACEBO	228	156.6	24.7	112	328	226	0.7	14.4	-52	80
		SB 207499	451	159.9	26.5	108	339	449	0.9	13.9	-44	48
	VISIT 3/WEEK 2	PLACEBO	218	157.0	24.8	96	332	217	0.7	14.5	-56	60
		SB 207499	442	159.1	27.1	108	339	440	0.3	14.2	-56	60
	VISIT 4/WEEK 4	PLACEBO	209	156.2	24.2	88	312	208	-0.0	13.9	-64	56
		SB 207499	449	159.8	25.8	108	312	447	0.9	14.3	-71	96
	VISIT 5/WEEK 8	PLACEBO	209	156.4	24.9	108	320	207	-0.3	14.2	-60	48
		SB 207499	437	159.3	26.9	96	300	435	0.6	13.6	-83	68
	VISIT 6/WEEK 12	PLACEBO	204	156.3	24.6	104	316	203	-0.5	14.5	-52	64
		SB 207499	435	159.9	30.9	104	539	434	1.1	19.3	-123	259
	VISIT 7/WEEK 16	PLACEBO	195	156.4	23.7	104	308	195	0.1	13.8	-56	48
		SB 207499	427	159.7	26.5	104	359	425	1.0	13.2	-32	76
	VISIT 8/WEEK 20	PLACEBO	192	155.6	24.4	100	312	191	-0.8	14.6	-64	40
		SB 207499	425	158.6	26.8	100	363	423	-0.1	13.9	-64	68
	VISIT 9/WEEK 24	PLACEBO	187	157.0	23.5	112	328	186	0.2	14.3	-64	52
		SB 207499	419	158.7	27.3	110	395	417	0.2	14.6	-56	68
	VISIT 10/WEEK 28	PLACEBO	186	157.3	24.6	100	332	185	0.6	14.9	-64	48
		SB 207499	414	159.0	25.7	112	323	412	0.8	14.1	-60	76
	VISIT 11/WEEK 32	PLACEBO	182	157.0	23.8	104	308	180	0.1	14.3	-56	56
		SB 207499	409	159.3	27.4	104	427	407	1.2	14.4	-60	68

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.18

DESCRIPTIVE STATISTICS FOR ECGS BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
PR (MSEC)	VISIT 12/WEEK 36	PLACEBO	182	157.9	25.1	104	332	181	0.9	13.3	-52	48
		SB 207499	401	158.3	27.1	104	420	399	-0.0	14.0	-44	60
	VISIT 13/WEEK 40	PLACEBO	181	157.8	25.5	100	352	180	0.3	14.5	-64	56
		SB 207499	397	158.4	27.2	104	400	395	0.1	14.2	-44	64
	VISIT 14/WEEK 44	PLACEBO	179	157.9	24.8	108	332	178	0.4	16.2	-72	52
		SB 207499	394	158.7	27.5	108	415	393	0.5	14.0	-48	80
	VISIT 15/WEEK 48	PLACEBO	178	157.6	26.2	100	352	177	0.2	14.3	-60	44
		SB 207499	388	159.4	27.9	108	427	387	1.2	13.9	-36	76
	VISIT 16/WEEK 52	PLACEBO	176	157.9	25.8	104	316	175	0.6	15.5	-64	48
		SB 207499	371	159.9	26.8	112	379	370	1.7	13.6	-40	60
	VISIT 17/WEEK 56	PLACEBO	165	158.7	26.3	112	340	164	1.3	16.1	-72	48
		SB 207499	354	159.4	25.1	100	268	353	1.2	13.6	-44	52
	VISIT 18/WEEK 60	PLACEBO	170	159.7	27.7	104	360	169	2.0	16.4	-64	56
		SB 207499	364	158.1	25.1	100	268	363	0.3	14.2	-52	60
	VISIT 19/WEEK 64	PLACEBO	140	158.1	25.2	112	332	139	0.8	15.7	-76	52
		SB 207499	299	160.0	24.1	112	268	298	1.7	13.3	-48	64
	VISIT 20/WEEK 68	PLACEBO	135	159.0	26.8	103	360	135	2.3	15.4	-35	60
		SB 207499	286	160.8	25.8	100	276	285	2.1	16.4	-52	68
	VISIT 21/WEEK 72	PLACEBO	167	158.1	26.3	88	360	166	1.0	15.9	-68	52
		SB 207499	346	159.5	25.5	104	284	345	1.2	15.2	-56	68
	VISIT 22/WEEK 76	PLACEBO	98	156.9	30.9	104	368	98	-0.3	17.4	-64	56
		SB 207499	190	158.3	24.0	104	264	190	-0.2	15.7	-40	68
	VISIT 23/WEEK 80	PLACEBO	95	157.6	29.3	100	352	95	0.2	14.7	-60	48
		SB 207499	187	158.9	25.9	116	280	186	0.2	15.3	-44	60
	VISIT 24/WEEK 84	PLACEBO	160	159.3	26.3	108	360	159	2.3	16.6	-76	64
		SB 207499	324	160.4	26.7	104	268	323	2.1	15.7	-44	76
	VISIT 25/WEEK 88	PLACEBO	50	158.6	36.4	104	364	50	1.3	14.4	-40	44
		SB 207499	92	162.5	29.6	112	288	92	1.0	17.1	-28	72
	VISIT 26/WEEK 92	PLACEBO	49	160.4	36.5	116	368	49	2.6	14.9	-36	48
		SB 207499	91	162.4	29.2	116	292	91	1.0	16.0	-32	76

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.18

DESCRIPTIVE STATISTICS FOR ECGS BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
PR (MSEC)	VISIT 27/WEEK 96	PLACEBO	157	159.3	28.1	108	396	156	2.2	16.0	-40	76
		SB 207499	319	159.9	26.1	104	272	318	1.7	15.5	-56	64
	VISIT 28/WEEK 100	PLACEBO	21	170.1	47.9	124	364	21	7.0	14.4	-20	44
		SB 207499	47	163.4	24.8	124	260	47	1.8	14.4	-32	44
	VISIT 29/WEEK 104	PLACEBO	18	169.3	54.5	120	372	18	7.3	16.2	-12	52
		SB 207499	39	164.3	28.3	128	268	39	1.4	14.3	-32	52
	VISIT 30/WEEK 108	PLACEBO	123	159.2	29.5	110	376	122	1.3	16.8	-60	56
		SB 207499	261	162.1	24.6	112	260	260	2.5	14.9	-65	72
	VISIT 31/WEEK 112	PLACEBO	9	177.8	76.5	124	376	9	12.0	19.4	-12	56
		SB 207499	18	171.1	38.3	132	280	18	4.2	19.5	-28	64
	VISIT 32/WEEK 116	PLACEBO	9	176.9	84.3	120	396	9	11.1	27.0	-16	76
		SB 207499	15	164.3	25.7	132	228	15	0.3	16.5	-36	24
	VISIT 33/WEEK 120	PLACEBO	87	158.0	30.2	120	363	87	0.4	16.3	-56	44
		SB 207499	179	161.1	26.7	116	280	179	1.5	16.2	-40	64
	VISIT 34/WEEK 124	PLACEBO	3	158.7	2.3	156	160	3	6.7	4.6	4	12
		SB 207499	3	166.7	9.2	156	172	3	-1.3	18.9	-16	20
QRS (MSEC)	VISIT 35/WEEK 128	PLACEBO	3	152.0	6.9	148	160	3	0.0	8.0	-8	8
		SB 207499	3	178.7	6.1	172	184	3	10.7	22.0	-4	36
	VISIT 36/WEEK 132	PLACEBO	35	154.6	16.2	120	188	35	-0.3	15.7	-60	24
		SB 207499	55	161.8	26.7	112	275	55	1.4	16.6	-48	40
	VISIT 37/WEEK 136	SB 207499	2	166.0	14.1	156	176	2	8.0	17.0	-4	20
		ENDPOINT	234	157.8	26.5	104	363	232	1.3	15.6	-60	52
	ENDPOINT	PLACEBO	234	157.8	26.5	104	363	232	1.3	15.6	-60	52
		SB 207499	465	161.1	32.1	112	539	462	2.0	18.7	-48	259
	BASELINE	PLACEBO	243	93.3	15.4	68	168	0	.	.	.	.
		SB 207499	480	92.9	15.6	64	176	0	.	.	.	.
QRS (MSEC)	VISIT 1/DAY 1	PLACEBO	243	94.3	16.4	60	168	243	1.0	7.8	-16	48
		SB 207499	480	93.3	16.1	64	176	480	0.4	7.9	-40	44
	VISIT 2/WEEK 1	PLACEBO	234	94.2	17.0	60	172	234	0.8	8.8	-24	52
		SB 207499	462	92.7	15.9	64	172	462	-0.2	8.2	-52	60

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.18

DESCRIPTIVE STATISTICS FOR ECGS BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
QRS (MSEC)	VISIT 3/WEEK 2	PLACEBO	223	94.0	16.3	60	172	223	0.7	7.9	-28	48
		SB 207499	452	93.3	16.8	64	164	452	0.3	8.5	-40	48
	VISIT 4/WEEK 4	PLACEBO	215	94.8	16.9	60	168	215	1.1	7.9	-20	44
		SB 207499	458	93.0	16.5	64	168	458	0.2	8.4	-32	56
	VISIT 5/WEEK 8	PLACEBO	213	93.4	16.4	60	164	213	-0.1	8.3	-24	48
		SB 207499	447	92.5	15.9	64	172	447	-0.5	7.5	-28	56
	VISIT 6/WEEK 12	PLACEBO	208	94.0	17.8	56	176	208	0.7	10.2	-28	84
		SB 207499	444	93.3	16.3	64	168	444	0.3	7.8	-28	60
	VISIT 7/WEEK 16	PLACEBO	202	94.4	16.9	60	168	202	1.0	9.3	-24	48
		SB 207499	436	93.0	16.1	64	156	436	0.1	7.9	-28	48
	VISIT 8/WEEK 20	PLACEBO	197	94.2	17.4	64	168	197	0.6	9.9	-24	60
		SB 207499	432	92.9	16.0	64	164	432	0.0	7.8	-28	44
	VISIT 9/WEEK 24	PLACEBO	193	93.8	16.3	64	164	193	0.1	8.8	-28	44
		SB 207499	427	92.7	15.8	64	164	427	0.0	7.9	-28	60
	VISIT 10/WEEK 28	PLACEBO	189	94.1	16.2	60	152	189	0.2	8.3	-24	48
		SB 207499	422	92.4	15.9	64	156	422	-0.4	7.9	-28	48
	VISIT 11/WEEK 32	PLACEBO	186	93.7	16.5	64	172	186	0.3	8.3	-24	40
		SB 207499	419	92.2	15.9	64	160	419	-0.5	8.0	-44	44
	VISIT 12/WEEK 36	PLACEBO	187	93.2	16.0	64	152	187	-0.3	8.3	-20	44
		SB 207499	410	93.3	15.1	60	160	410	0.4	7.7	-28	44
	VISIT 13/WEEK 40	PLACEBO	185	93.7	15.8	64	168	185	0.2	8.3	-24	44
		SB 207499	405	92.6	16.1	60	164	405	-0.1	8.2	-32	60
	VISIT 14/WEEK 44	PLACEBO	183	93.7	16.5	56	164	183	0.2	8.2	-20	40
		SB 207499	404	92.6	16.1	64	164	404	0.0	8.3	-28	56
	VISIT 15/WEEK 48	PLACEBO	184	92.7	16.3	56	168	184	-0.8	8.1	-20	36
		SB 207499	397	92.8	15.8	64	164	397	0.0	8.0	-28	52
	VISIT 16/WEEK 52	PLACEBO	180	94.0	16.7	60	164	180	0.4	8.8	-20	52
		SB 207499	384	92.9	16.3	56	164	384	0.5	8.7	-28	52
	VISIT 17/WEEK 56	PLACEBO	169	93.8	16.3	60	160	169	0.2	8.2	-16	40
		SB 207499	364	92.7	16.5	64	168	364	0.1	9.1	-32	60

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

SB 207499

TABLE 15.18

DESCRIPTIVE STATISTICS FOR ECGS BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
QRS (MSEC)	VISIT 18/WEEK 60	PLACEBO	173	93.7	16.8	60	164	173	0.2	8.2	-28	44
		SB 207499	374	93.4	17.0	60	160	374	0.3	8.9	-32	52
	VISIT 19/WEEK 64	PLACEBO	142	93.5	16.0	64	156	142	0.5	9.6	-20	44
		SB 207499	308	92.5	17.1	60	176	308	0.5	9.1	-28	52
	VISIT 20/WEEK 68	PLACEBO	140	93.4	16.1	68	156	140	0.2	8.6	-20	40
		SB 207499	295	92.6	16.7	64	160	295	0.5	9.3	-48	48
	VISIT 21/WEEK 72	PLACEBO	170	93.5	15.9	64	152	170	0.1	8.3	-24	40
		SB 207499	357	92.9	17.3	60	168	357	-0.3	9.0	-32	48
	VISIT 22/WEEK 76	PLACEBO	100	90.8	14.6	64	152	100	-0.5	8.2	-24	20
		SB 207499	198	91.2	16.2	64	164	198	0.2	9.1	-28	48
	VISIT 23/WEEK 80	PLACEBO	98	91.1	15.2	60	152	98	-0.2	7.8	-16	20
		SB 207499	193	91.9	16.3	56	164	193	1.0	10.3	-24	68
	VISIT 24/WEEK 84	PLACEBO	163	93.4	15.9	60	168	163	-0.0	8.5	-24	48
		SB 207499	334	93.2	17.3	60	176	334	0.2	10.0	-24	48
	VISIT 25/WEEK 88	PLACEBO	53	90.0	13.8	60	136	53	0.3	7.8	-16	20
		SB 207499	97	92.8	16.0	68	152	97	0.9	10.8	-24	48
	VISIT 26/WEEK 92	PLACEBO	52	91.9	15.6	60	140	52	2.0	9.5	-12	32
		SB 207499	96	91.8	16.8	68	152	96	-0.2	11.0	-24	48
	VISIT 27/WEEK 96	PLACEBO	160	95.0	16.8	60	164	160	1.2	8.6	-17	48
		SB 207499	328	93.3	18.0	64	176	328	-0.1	10.4	-36	60
	VISIT 28/WEEK 100	PLACEBO	22	92.8	12.9	76	116	22	3.7	6.9	-8	20
		SB 207499	49	91.1	15.8	68	144	49	0.6	11.9	-16	56
	VISIT 29/WEEK 104	PLACEBO	18	92.9	14.6	72	124	18	4.9	7.5	-4	20
		SB 207499	40	90.5	13.6	76	136	40	1.2	11.2	-16	48
	VISIT 30/WEEK 108	PLACEBO	126	96.0	17.5	60	164	126	1.6	10.5	-24	44
		SB 207499	272	93.8	18.8	60	172	272	0.2	10.3	-20	60
	VISIT 31/WEEK 112	PLACEBO	9	95.6	11.2	80	112	9	5.3	7.2	-8	16
		SB 207499	18	91.1	15.0	72	132	18	0.7	6.0	-16	8
	VISIT 32/WEEK 116	PLACEBO	9	99.6	17.0	76	136	9	9.3	19.0	-8	56
		SB 207499	16	91.8	14.7	72	136	16	0.3	7.7	-12	16

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

SB 207499

TABLE 15.18

DESCRIPTIVE STATISTICS FOR ECGS BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
QRS (MSEC)	VISIT 33/WEEK 120	PLACEBO	91	96.1	17.3	68	168	91	0.9	10.3	-24	52
		SB 207499	187	92.5	17.8	60	168	187	0.4	9.6	-24	56
	VISIT 34/WEEK 124	PLACEBO	3	85.3	4.6	80	88	3	-1.3	2.3	-4	0
		SB 207499	3	93.3	23.4	76	120	3	-1.3	12.2	-12	12
	VISIT 35/WEEK 128	PLACEBO	3	97.3	4.6	92	100	3	10.7	2.3	8	12
		SB 207499	3	84.0	18.3	68	104	3	-10.7	6.1	-16	-4
	VISIT 36/WEEK 132	PLACEBO	36	91.4	10.0	68	112	36	-1.1	9.5	-16	24
		SB 207499	58	93.0	17.3	68	156	58	-0.2	7.6	-20	16
	VISIT 37/WEEK 136	PLACEBO	1	100.0	.	100	100	1	20.0	.	20	20
		SB 207499	2	78.0	8.5	72	84	2	-10.0	2.8	-12	-8
	ENDPOINT	PLACEBO	239	93.8	17.3	60	168	239	0.4	9.0	-24	44
		SB 207499	471	93.3	17.5	64	172	471	0.5	10.1	-32	72
Uncorrected QT (MSEC)	BASELINE	PLACEBO	243	384.1	29.0	308	480	0	.	.	.	.
		SB 207499	480	385.4	32.7	304	516	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	243	380.1	31.1	292	472	243	-3.9	25.6	-100	64
		SB 207499	480	381.7	32.5	300	524	480	-3.7	26.1	-132	88
	VISIT 2/WEEK 1	PLACEBO	234	380.8	32.2	296	484	234	-2.6	27.2	-116	88
		SB 207499	462	381.8	33.1	296	500	462	-4.0	28.8	-136	96
	VISIT 3/WEEK 2	PLACEBO	223	383.7	31.6	296	460	223	0.1	27.3	-128	88
		SB 207499	452	381.7	33.0	304	500	452	-4.1	28.9	-148	88
	VISIT 4/WEEK 4	PLACEBO	215	380.1	33.3	292	476	215	-3.3	27.9	-128	72
		SB 207499	458	381.5	32.2	300	528	458	-3.9	26.3	-112	88
	VISIT 5/WEEK 8	PLACEBO	213	378.7	32.1	304	484	213	-4.8	27.8	-116	60
		SB 207499	447	382.1	33.9	296	492	447	-3.7	27.9	-132	92
	VISIT 6/WEEK 12	PLACEBO	208	380.6	32.2	304	472	208	-3.2	29.3	-132	96
		SB 207499	444	382.2	34.2	292	528	444	-3.4	27.7	-124	100
	VISIT 7/WEEK 16	PLACEBO	202	379.7	32.7	304	484	202	-3.7	29.9	-128	104
		SB 207499	436	380.2	34.7	288	572	436	-5.0	27.9	-184	104
	VISIT 8/WEEK 20	PLACEBO	197	379.8	35.4	292	488	197	-3.4	31.4	-128	124
		SB 207499	432	380.0	35.1	284	612	432	-5.0	26.6	-108	144

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

SB 207499

TABLE 15.18

DESCRIPTIVE STATISTICS FOR ECGS BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Uncorrected QT (MSEC)	VISIT 9/WEEK 24	PLACEBO	193	378.2	32.1	300	480	193	-4.5	28.7	-128	84
		SB 207499	427	381.1	34.4	288	584	427	-3.6	28.6	-156	116
	VISIT 10/WEEK 28	PLACEBO	190	379.6	33.1	312	484	190	-3.7	29.4	-120	84
		SB 207499	422	380.7	34.3	296	600	422	-4.2	27.3	-104	132
	VISIT 11/WEEK 32	PLACEBO	186	379.4	32.8	280	472	186	-3.2	30.8	-136	80
		SB 207499	419	380.1	34.9	296	596	419	-4.8	28.7	-168	128
	VISIT 12/WEEK 36	PLACEBO	187	379.9	34.0	308	496	187	-2.8	31.2	-148	92
		SB 207499	410	381.1	34.1	308	548	410	-4.1	28.0	-124	88
	VISIT 13/WEEK 40	PLACEBO	185	381.4	32.1	300	512	185	-1.2	30.3	-132	124
		SB 207499	405	380.8	34.2	308	572	405	-4.4	27.4	-156	104
	VISIT 14/WEEK 44	PLACEBO	183	378.3	34.2	300	516	183	-4.0	32.2	-136	84
		SB 207499	404	380.9	34.7	296	564	404	-4.3	28.5	-120	96
	VISIT 15/WEEK 48	PLACEBO	184	378.8	34.8	260	524	184	-3.5	29.8	-116	88
		SB 207499	396	382.3	34.6	308	544	396	-2.6	26.5	-104	76
	VISIT 16/WEEK 52	PLACEBO	180	378.6	33.1	296	508	180	-3.9	28.7	-132	108
		SB 207499	383	380.6	32.0	300	532	383	-4.3	27.7	-124	92
	VISIT 17/WEEK 56	PLACEBO	169	378.7	34.4	288	496	169	-4.0	31.1	-140	100
		SB 207499	364	378.7	32.7	260	504	364	-6.2	30.0	-160	76
	VISIT 18/WEEK 60	PLACEBO	173	379.8	34.6	276	484	173	-2.8	30.9	-136	96
		SB 207499	373	378.6	34.1	304	580	373	-6.4	28.9	-148	112
	VISIT 19/WEEK 64	PLACEBO	142	378.6	35.8	300	496	142	-4.4	32.9	-140	116
		SB 207499	308	378.6	34.3	296	504	308	-4.1	26.9	-112	112
	VISIT 20/WEEK 68	PLACEBO	140	377.7	33.6	296	508	140	-5.2	30.1	-144	84
		SB 207499	295	379.3	32.7	300	516	295	-3.2	26.8	-84	104
	VISIT 21/WEEK 72	PLACEBO	170	378.9	34.7	292	504	170	-3.7	30.8	-136	88
		SB 207499	357	382.4	35.2	288	580	357	-3.0	31.2	-104	152
	VISIT 22/WEEK 76	PLACEBO	100	376.2	33.1	296	452	100	-5.1	33.1	-144	92
		SB 207499	198	376.1	30.7	296	460	198	-4.9	27.0	-172	60
	VISIT 23/WEEK 80	PLACEBO	98	376.1	33.7	296	484	98	-4.9	32.1	-144	104
		SB 207499	193	379.4	33.0	316	500	193	-1.8	28.2	-100	96

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

SB 207499

TABLE 15.18

DESCRIPTIVE STATISTICS FOR ECGS BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Uncorrected QT (MSEC)	VISIT 24/WEEK 84	PLACEBO	163	379.1	34.3	292	504	163	-3.5	31.0	-148	96
		SB 207499	334	382.2	34.0	296	548	334	-3.2	28.3	-136	80
	VISIT 25/WEEK 88	PLACEBO	53	375.8	37.0	300	448	53	-1.1	37.2	-136	104
		SB 207499	97	378.1	33.8	308	480	97	-3.3	26.2	-84	64
	VISIT 26/WEEK 92	PLACEBO	52	380.7	39.1	312	504	52	4.3	37.3	-136	96
		SB 207499	96	378.7	36.8	308	512	96	-3.0	26.5	-72	64
	VISIT 27/WEEK 96	PLACEBO	160	380.8	33.7	308	500	160	-2.3	32.1	-140	112
		SB 207499	328	381.7	33.6	292	516	328	-4.5	28.2	-112	80
	VISIT 28/WEEK 100	PLACEBO	22	373.3	32.1	316	432	22	6.7	28.0	-20	116
		SB 207499	49	379.4	33.8	320	456	49	-0.1	28.1	-56	72
	VISIT 29/WEEK 104	PLACEBO	18	379.3	40.4	296	444	18	13.8	38.0	-20	100
		SB 207499	39	378.6	32.6	328	444	39	2.4	25.0	-40	60
	VISIT 30/WEEK 108	PLACEBO	126	380.4	36.4	308	504	126	-1.7	31.0	-76	92
		SB 207499	272	382.9	32.9	296	492	272	-2.3	27.8	-100	68
	VISIT 31/WEEK 112	PLACEBO	9	394.4	24.0	368	440	9	17.1	36.0	-28	96
		SB 207499	18	374.7	36.9	320	464	18	4.0	26.0	-28	56
	VISIT 32/WEEK 116	PLACEBO	9	399.6	28.2	356	432	9	22.2	47.0	-28	116
		SB 207499	15	375.2	35.6	328	440	15	2.4	23.0	-28	56
	VISIT 33/WEEK 120	PLACEBO	91	380.9	34.6	300	500	91	-1.9	32.0	-80	96
		SB 207499	187	378.8	34.1	300	480	187	-4.4	31.0	-108	92
	VISIT 34/WEEK 124	PLACEBO	3	394.7	42.8	348	432	3	24.0	27.7	-8	40
		SB 207499	3	373.3	34.5	336	404	3	-8.0	10.6	-20	0
	VISIT 35/WEEK 128	PLACEBO	3	382.7	30.0	352	412	3	12.0	13.9	-4	20
		SB 207499	3	362.7	37.2	320	388	3	-18.7	16.2	-36	-4
	VISIT 36/WEEK 132	PLACEBO	36	380.6	35.5	324	464	36	-2.3	36.4	-76	84
		SB 207499	58	376.6	38.1	316	508	58	-0.7	32.4	-96	68
	VISIT 37/WEEK 136	PLACEBO	1	364.0	.	364	364	1	8.0	.	8	8
		SB 207499	2	356.0	45.3	324	388	2	-14.0	25.5	-32	4
ENDPOINT		PLACEBO	239	378.1	34.3	300	500	239	-5.7	30.3	-140	84
		SB 207499	471	379.8	35.6	292	540	471	-6.0	32.4	-132	152

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.18

DESCRIPTIVE STATISTICS FOR ECGS BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Corrected QT (MSEC)	BASELINE	PLACEBO	243	423.1	22.0	382	532	0	.	.	.	.
		SB 207499	480	424.1	21.6	371	521	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	243	421.7	22.8	376	508	243	-1.4	19.4	-69	99
		SB 207499	480	423.8	22.2	378	515	480	-0.3	19.0	-118	63
	VISIT 2/WEEK 1	PLACEBO	234	422.7	22.3	381	522	234	-0.8	18.1	-59	65
		SB 207499	462	422.3	20.7	373	514	462	-1.7	19.0	-132	70
	VISIT 3/WEEK 2	PLACEBO	223	423.1	21.5	380	508	223	-0.4	19.3	-82	74
		SB 207499	452	422.1	20.3	371	497	452	-2.1	18.8	-130	55
	VISIT 4/WEEK 4	PLACEBO	215	423.0	23.2	373	536	215	-0.9	18.0	-77	64
		SB 207499	458	422.2	22.0	373	510	458	-1.8	19.2	-125	71
	VISIT 5/WEEK 8	PLACEBO	213	421.2	20.9	372	520	213	-2.8	18.4	-97	48
		SB 207499	447	422.1	21.4	367	522	447	-2.0	19.0	-121	68
	VISIT 6/WEEK 12	PLACEBO	208	423.3	23.2	376	530	208	-0.7	20.1	-82	76
		SB 207499	444	421.9	21.4	372	504	444	-2.2	19.7	-124	54
	VISIT 7/WEEK 16	PLACEBO	202	422.0	20.7	383	505	202	-1.8	18.8	-91	56
		SB 207499	436	421.6	20.8	357	510	436	-2.4	19.9	-135	71
	VISIT 8/WEEK 20	PLACEBO	197	424.8	22.9	378	519	197	1.4	19.6	-77	62
		SB 207499	432	422.0	21.9	376	531	432	-1.8	18.4	-110	69
	VISIT 9/WEEK 24	PLACEBO	193	422.3	21.5	376	509	193	-1.1	19.7	-96	64
		SB 207499	427	421.6	19.7	374	485	427	-2.1	19.4	-141	50
	VISIT 10/WEEK 28	PLACEBO	190	424.6	22.2	383	511	190	0.8	18.6	-69	59
		SB 207499	422	421.7	21.4	372	511	422	-2.2	19.8	-149	62
	VISIT 11/WEEK 32	PLACEBO	186	422.3	24.0	341	496	186	-0.6	19.8	-89	73
		SB 207499	419	421.6	20.9	368	513	419	-2.2	19.2	-118	59
	VISIT 12/WEEK 36	PLACEBO	187	421.6	22.6	361	495	187	-1.3	21.7	-96	96
		SB 207499	410	421.8	20.1	378	497	410	-2.2	19.7	-142	57
	VISIT 13/WEEK 40	PLACEBO	185	423.7	24.4	371	602	185	0.9	21.7	-113	135
		SB 207499	405	421.5	20.8	366	495	405	-2.7	19.3	-132	53
	VISIT 14/WEEK 44	PLACEBO	183	422.7	20.4	373	488	183	-0.2	18.1	-99	57
		SB 207499	404	423.3	21.7	366	514	404	-0.7	19.7	-125	73

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.18

DESCRIPTIVE STATISTICS FOR ECGS BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Corrected QT (MSEC)	VISIT 15/WEEK 48	PLACEBO	184	422.1	21.1	378	493	184	-0.7	18.7	-79	53
		SB 207499	396	422.0	20.8	367	506	396	-1.8	18.8	-131	57
	VISIT 16/WEEK 52	PLACEBO	180	422.3	21.5	374	493	180	-0.4	18.3	-91	58
		SB 207499	383	421.9	20.7	353	523	383	-2.2	20.1	-136	86
	VISIT 17/WEEK 56	PLACEBO	169	423.2	22.5	375	487	169	0.6	19.8	-106	60
		SB 207499	364	422.7	23.1	377	545	364	-1.5	21.3	-144	121
	VISIT 18/WEEK 60	PLACEBO	173	423.0	23.0	343	499	173	-0.0	20.5	-96	52
		SB 207499	373	423.1	21.7	368	509	373	-1.0	20.1	-153	88
	VISIT 19/WEEK 64	PLACEBO	142	421.5	21.3	372	506	142	-1.1	21.7	-99	85
		SB 207499	308	423.0	22.1	377	518	308	-1.6	19.9	-144	72
	VISIT 20/WEEK 68	PLACEBO	140	420.9	20.1	385	493	140	-1.8	20.7	-113	53
		SB 207499	295	423.2	21.7	380	496	295	-1.4	18.9	-109	54
	VISIT 21/WEEK 72	PLACEBO	170	421.4	20.9	366	497	170	-1.8	20.5	-103	61
		SB 207499	357	423.4	22.5	366	553	357	-0.7	18.7	-116	78
	VISIT 22/WEEK 76	PLACEBO	100	421.4	23.9	385	500	100	-1.6	22.1	-78	58
		SB 207499	198	421.7	19.0	387	496	198	0.3	16.8	-54	72
	VISIT 23/WEEK 80	PLACEBO	98	420.1	21.3	376	496	98	-2.6	21.0	-104	55
		SB 207499	193	423.1	22.2	369	511	193	2.0	19.7	-47	87
	VISIT 24/WEEK 84	PLACEBO	163	421.9	21.8	373	492	163	-1.1	20.9	-87	72
		SB 207499	334	422.6	21.1	354	494	334	-1.4	19.3	-121	57
	VISIT 25/WEEK 88	PLACEBO	53	418.1	17.8	390	479	53	-1.1	21.4	-89	51
		SB 207499	97	418.4	18.1	389	468	97	-1.2	17.5	-61	50
	VISIT 26/WEEK 92	PLACEBO	52	420.8	22.9	378	491	52	2.0	25.7	-101	53
		SB 207499	96	420.3	19.3	380	476	96	0.2	17.3	-54	43
	VISIT 27/WEEK 96	PLACEBO	160	423.1	22.2	374	487	160	-0.0	20.0	-88	64
		SB 207499	328	424.5	22.7	362	500	328	-0.0	20.9	-140	95
	VISIT 28/WEEK 100	PLACEBO	22	413.1	18.9	387	462	22	-0.6	14.3	-27	29
		SB 207499	49	420.7	19.1	387	478	49	0.5	16.5	-40	54
	VISIT 29/WEEK 104	PLACEBO	18	413.3	13.4	398	440	18	1.4	16.1	-29	36
		SB 207499	39	423.3	20.9	385	482	39	2.7	20.2	-37	63

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.18

DESCRIPTIVE STATISTICS FOR ECGS BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Corrected QT (MSEC)	VISIT 30/WEEK 108	PLACEBO	126	424.9	23.0	386	497	126	1.8	20.2	-54	60
		SB 207499	272	424.9	22.8	361	515	272	-0.7	20.1	-121	77
	VISIT 31/WEEK 112	PLACEBO	9	410.0	9.6	396	426	9	-0.9	7.3	-14	12
		SB 207499	18	423.6	20.6	386	471	18	-1.6	16.0	-26	30
	VISIT 32/WEEK 116	PLACEBO	9	417.4	20.3	398	459	9	6.5	26.5	-31	47
		SB 207499	15	425.9	20.0	392	463	15	-0.9	13.4	-26	16
	VISIT 33/WEEK 120	PLACEBO	91	424.3	21.6	391	493	91	2.5	16.6	-32	59
		SB 207499	187	424.5	23.0	359	515	187	-0.8	21.2	-133	52
	VISIT 34/WEEK 124	PLACEBO	3	419.6	18.9	402	440	3	15.0	12.0	1	22
		SB 207499	3	438.0	37.2	405	478	3	9.2	24.5	-13	35
	VISIT 35/WEEK 128	PLACEBO	3	437.8	8.8	429	446	3	33.3	8.7	28	43
		SB 207499	3	426.4	32.3	398	462	3	-2.4	23.7	-28	19
	VISIT 36/WEEK 132	PLACEBO	36	420.8	19.7	397	477	36	-0.8	18.9	-36	49
		SB 207499	58	426.9	23.9	388	500	58	4.4	15.0	-26	46
	VISIT 37/WEEK 136	PLACEBO	1	412.4	.	412	412	1	11.7	.	12	12
		SB 207499	2	415.2	7.4	410	420	2	-6.8	1.3	-8	-6
	ENDPOINT	PLACEBO	239	424.3	23.2	386	511	239	1.1	18.9	-88	60
		SB 207499	471	424.6	23.1	359	553	471	0.6	20.8	-133	78
Axis (DEG)	BASELINE	PLACEBO	243	33.2	48.6	-171	164	0	.	.	.	.
		SB 207499	480	37.2	46.9	-161	147	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	243	33.2	46.9	-156	148	243	-0.0	28.6	-146	167
		SB 207499	480	36.3	47.7	-159	148	480	-0.9	25.7	-236	164
	VISIT 2/WEEK 1	PLACEBO	234	35.3	45.9	-127	172	234	2.1	26.8	-92	176
		SB 207499	462	36.2	47.6	-179	144	462	-0.9	25.3	-223	192
	VISIT 3/WEEK 2	PLACEBO	223	33.2	45.7	-137	146	223	-1.0	25.2	-143	162
		SB 207499	452	35.6	50.1	-175	139	452	-1.8	29.6	-245	164
	VISIT 4/WEEK 4	PLACEBO	215	32.3	46.4	-140	129	215	-1.5	26.8	-146	159
		SB 207499	458	37.3	48.2	-161	167	458	-0.3	24.5	-228	162
	VISIT 5/WEEK 8	PLACEBO	213	31.2	45.6	-126	122	213	-1.9	25.2	-132	162
		SB 207499	447	37.9	46.2	-165	148	447	0.0	25.4	-219	149

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.18

DESCRIPTIVE STATISTICS FOR ECGS BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Axis (DEG)	VISIT 6/WEEK 12	PLACEBO	208	33.6	49.7	-169	179	208	0.2	26.7	-175	157
		SB 207499	443	37.4	46.2	-165	142	443	-0.1	23.4	-235	162
	VISIT 7/WEEK 16	PLACEBO	202	32.0	47.0	-164	122	202	-1.0	28.3	-136	159
		SB 207499	435	38.6	45.7	-159	156	435	0.7	24.5	-236	160
	VISIT 8/WEEK 20	PLACEBO	197	33.6	46.5	-120	110	197	0.9	28.7	-165	170
		SB 207499	432	36.7	47.0	-158	136	432	-1.2	25.8	-236	141
	VISIT 9/WEEK 24	PLACEBO	193	31.8	46.6	-113	118	193	-1.0	27.2	-145	160
		SB 207499	427	36.5	47.5	-163	145	427	-1.3	26.0	-248	161
	VISIT 10/WEEK 28	PLACEBO	190	31.2	46.3	-113	128	190	-1.2	29.5	-126	158
		SB 207499	422	36.4	47.9	-165	170	422	-1.3	27.2	-227	169
	VISIT 11/WEEK 32	PLACEBO	186	30.5	48.5	-154	124	186	-1.6	30.1	-154	158
		SB 207499	419	37.4	47.6	-167	159	419	-0.1	30.0	-230	213
	VISIT 12/WEEK 36	PLACEBO	187	29.2	49.5	-166	118	187	-3.2	34.5	-262	165
		SB 207499	410	35.2	47.9	-175	154	410	-2.8	28.4	-237	157
	VISIT 13/WEEK 40	PLACEBO	185	33.8	49.5	-152	155	185	1.8	35.0	-151	226
		SB 207499	405	36.2	48.7	-174	170	405	-0.8	28.3	-220	176
	VISIT 14/WEEK 44	PLACEBO	183	31.5	46.5	-138	119	183	-0.7	28.9	-163	155
		SB 207499	403	35.9	48.9	-170	176	403	-1.6	27.8	-192	161
	VISIT 15/WEEK 48	PLACEBO	184	33.3	47.1	-136	134	184	1.4	28.5	-111	157
		SB 207499	397	36.0	46.8	-160	143	397	-1.8	26.9	-229	143
	VISIT 16/WEEK 52	PLACEBO	179	31.1	47.6	-120	127	179	-0.6	30.5	-216	158
		SB 207499	384	33.8	50.0	-166	168	384	-3.0	30.7	-236	146
	VISIT 17/WEEK 56	PLACEBO	169	31.6	49.2	-118	166	169	-0.0	30.6	-129	155
		SB 207499	364	33.0	51.6	-173	170	364	-4.5	34.4	-231	156
	VISIT 18/WEEK 60	PLACEBO	173	34.7	48.8	-151	155	173	2.2	33.7	-157	181
		SB 207499	374	33.9	50.8	-170	169	374	-3.5	31.8	-248	176
	VISIT 19/WEEK 64	PLACEBO	142	31.7	45.8	-117	168	142	0.8	30.0	-103	153
		SB 207499	308	32.6	51.3	-162	142	308	-3.2	29.2	-224	148
	VISIT 20/WEEK 68	PLACEBO	140	31.7	48.3	-162	144	140	1.4	34.8	-258	154
		SB 207499	295	34.5	51.2	-169	175	295	-1.1	29.3	-191	138

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

SB 207499

TABLE 15.18

DESCRIPTIVE STATISTICS FOR ECGS BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Axis (DEG)	VISIT 21/WEEK 72	PLACEBO	170	33.0	48.2	-117	142	170	1.0	31.9	-140	180
		SB 207499	356	33.3	50.0	-178	147	356	-3.8	30.8	-205	139
	VISIT 22/WEEK 76	PLACEBO	100	32.3	45.3	-136	121	100	1.9	32.5	-102	156
		SB 207499	198	37.5	44.8	-90	144	198	-0.2	24.2	-90	131
	VISIT 23/WEEK 80	PLACEBO	98	32.1	45.9	-122	127	98	1.7	30.8	-119	159
		SB 207499	193	34.5	51.4	-175	114	193	-2.9	35.1	-234	138
	VISIT 24/WEEK 84	PLACEBO	163	33.1	45.4	-111	140	163	0.7	29.2	-128	155
		SB 207499	334	35.2	48.1	-168	146	334	-1.0	29.4	-153	224
	VISIT 25/WEEK 88	PLACEBO	53	34.3	41.7	-73	133	53	6.9	38.7	-84	156
		SB 207499	97	39.0	47.8	-76	153	97	6.0	34.5	-81	172
	VISIT 26/WEEK 92	PLACEBO	52	28.9	43.6	-73	122	52	2.5	39.7	-97	156
		SB 207499	96	34.5	49.1	-118	151	96	1.9	27.5	-82	131
	VISIT 27/WEEK 96	PLACEBO	160	32.7	48.9	-118	171	160	1.1	31.4	-134	157
		SB 207499	325	32.0	52.1	-175	139	325	-3.9	33.9	-226	226
	VISIT 28/WEEK 100	PLACEBO	22	48.3	39.3	-50	112	22	12.8	37.3	-20	154
		SB 207499	49	34.3	45.8	-85	109	49	3.6	29.2	-45	128
	VISIT 29/WEEK 104	PLACEBO	18	51.7	31.8	-17	85	18	17.3	40.8	-21	154
		SB 207499	40	32.8	46.4	-81	85	40	1.2	24.1	-41	101
	VISIT 30/WEEK 108	PLACEBO	126	32.0	49.4	-123	123	126	0.3	32.1	-98	154
		SB 207499	271	31.5	51.3	-151	174	271	-1.8	32.9	-169	225
	VISIT 31/WEEK 112	PLACEBO	9	60.7	45.0	13	165	9	23.0	43.5	-7	121
		SB 207499	18	41.3	36.4	-33	85	18	6.9	30.1	-25	92
	VISIT 32/WEEK 116	PLACEBO	9	43.3	41.2	-47	83	9	5.7	14.7	-22	26
		SB 207499	16	45.8	33.6	-38	85	16	5.9	27.2	-17	95
	VISIT 33/WEEK 120	PLACEBO	91	30.7	46.2	-127	130	91	2.5	30.1	-82	157
		SB 207499	187	32.3	46.9	-86	143	187	-2.9	28.6	-150	122
	VISIT 34/WEEK 124	PLACEBO	3	67.3	14.6	57	84	3	6.3	6.5	0	13
		SB 207499	3	5.0	58.4	-43	70	3	-4.7	6.0	-11	1
	VISIT 35/WEEK 128	PLACEBO	3	68.0	11.5	57	80	3	7.0	14.2	-4	23
		SB 207499	3	8.7	56.9	-38	72	3	-1.0	4.6	-6	3

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

SB 207499

TABLE 15.18

DESCRIPTIVE STATISTICS FOR ECGS BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
Axis (DEG)	VISIT 36/WEEK 132	PLACEBO	36	32.3	39.9	-62	104	36	4.4	37.2	-81	165
		SB 207499	58	30.9	46.3	-136	105	58	-3.8	30.2	-99	123
	VISIT 37/WEEK 136	PLACEBO	1	63.0	.	63	63	1	8.0	.	8	8
		SB 207499	2	16.5	81.3	-41	74	2	-2.0	9.9	-9	5
	ENDPOINT	PLACEBO	239	31.9	48.8	-151	168	239	-1.6	28.4	-157	165
		SB 207499	471	33.8	49.9	-175	150	471	-3.9	30.4	-234	225
RR (MSEC)	BASELINE	PLACEBO	243	832.5	136.2	541	1200	0	.	.	.	.
		SB 207499	480	834.8	149.1	550	1463	0	.	.	.	.
	VISIT 1/DAY 1	PLACEBO	243	821.8	143.2	458	1250	243	-10.7	110.5	-400	337
		SB 207499	480	819.2	141.7	517	1500	480	-15.6	121.6	-659	452
	VISIT 2/WEEK 1	PLACEBO	234	820.1	142.0	492	1304	234	-8.4	116.1	-434	325
		SB 207499	462	826.0	146.6	492	1395	462	-10.9	136.2	-616	455
	VISIT 3/WEEK 2	PLACEBO	223	830.6	139.4	531	1200	223	1.4	121.3	-450	394
		SB 207499	452	826.0	145.1	488	1364	452	-10.2	134.9	-721	452
	VISIT 4/WEEK 4	PLACEBO	215	816.9	149.5	426	1250	215	-9.8	121.6	-458	345
		SB 207499	458	825.6	145.4	484	1500	458	-9.9	125.6	-600	495
	VISIT 5/WEEK 8	PLACEBO	213	816.5	140.8	480	1176	213	-10.4	118.0	-507	314
		SB 207499	447	829.1	155.1	488	1395	447	-7.8	130.1	-588	541
	VISIT 6/WEEK 12	PLACEBO	208	817.9	145.5	508	1277	208	-10.3	125.8	-544	341
		SB 207499	444	829.9	152.8	513	1500	444	-5.9	125.6	-594	495
	VISIT 7/WEEK 16	PLACEBO	202	818.4	148.1	536	1333	202	-8.4	123.9	-480	373
		SB 207499	436	821.7	151.3	492	1622	436	-12.5	126.0	-764	490
	VISIT 8/WEEK 20	PLACEBO	197	808.8	154.3	500	1333	197	-18.9	135.9	-532	479
		SB 207499	432	819.8	154.2	504	1714	432	-14.5	121.3	-450	582
	VISIT 9/WEEK 24	PLACEBO	193	810.6	142.6	405	1250	193	-14.6	126.0	-538	374
		SB 207499	427	826.2	155.1	492	1667	427	-7.4	131.1	-606	535
	VISIT 10/WEEK 28	PLACEBO	190	809.5	153.5	462	1304	190	-17.2	123.8	-458	331
		SB 207499	422	823.0	146.9	472	1667	422	-10.6	128.6	-459	552
	VISIT 11/WEEK 32	PLACEBO	186	816.4	146.8	513	1250	186	-10.7	128.5	-555	331
		SB 207499	419	821.5	153.9	496	1714	419	-12.1	130.1	-713	582

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

SB 207499

TABLE 15.18

DESCRIPTIVE STATISTICS FOR ECGS BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
RR (MSEC)	VISIT 12/WEEK 36	PLACEBO	187	821.5	149.2	411	1200	187	-5.8	131.3	-544	388
		SB 207499	410	824.3	148.9	496	1500	410	-10.3	129.2	-480	382
	VISIT 13/WEEK 40	PLACEBO	185	818.8	141.0	541	1250	185	-8.3	120.8	-501	312
		SB 207499	405	824.8	147.7	500	1463	405	-9.5	127.9	-694	359
	VISIT 14/WEEK 44	PLACEBO	183	810.9	159.6	451	1463	183	-14.5	148.5	-566	396
		SB 207499	404	818.4	152.3	432	1622	404	-16.0	133.3	-659	490
	VISIT 15/WEEK 48	PLACEBO	184	815.6	158.2	472	1500	184	-10.4	133.9	-494	371
		SB 207499	398	828.8	152.1	492	1538	398	-5.7	127.6	-479	406
	VISIT 16/WEEK 52	PLACEBO	180	813.1	150.6	513	1395	180	-14.1	130.7	-526	471
		SB 207499	384	821.4	143.3	536	1463	384	-11.4	129.4	-581	422
	VISIT 17/WEEK 56	PLACEBO	169	808.9	146.9	526	1333	169	-19.5	120.7	-402	345
		SB 207499	364	811.7	147.4	462	1395	364	-20.5	138.2	-694	345
	VISIT 18/WEEK 60	PLACEBO	173	816.6	156.7	462	1333	173	-9.7	135.2	-501	453
		SB 207499	374	809.4	148.8	496	1500	374	-24.4	135.8	-618	464
	VISIT 19/WEEK 64	PLACEBO	142	815.1	150.8	550	1333	142	-13.7	134.5	-450	479
		SB 207499	308	809.5	147.7	522	1395	308	-12.1	126.9	-566	554
	VISIT 20/WEEK 68	PLACEBO	140	813.3	148.2	531	1395	140	-14.4	125.4	-343	366
		SB 207499	295	812.0	145.3	472	1463	295	-8.8	119.1	-377	487
	VISIT 21/WEEK 72	PLACEBO	170	816.9	151.8	500	1395	170	-8.8	125.5	-601	350
		SB 207499	357	825.1	160.0	472	1714	357	-10.0	140.1	-527	582
	VISIT 22/WEEK 76	PLACEBO	100	808.5	156.8	488	1176	100	-12.2	148.6	-395	494
		SB 207499	198	804.0	140.7	508	1176	198	-21.8	129.2	-768	337
	VISIT 23/WEEK 80	PLACEBO	98	812.6	163.8	561	1304	98	-7.8	136.7	-344	436
		SB 207499	193	812.8	146.8	508	1277	193	-15.3	126.3	-401	500
	VISIT 24/WEEK 84	PLACEBO	163	816.9	151.3	504	1224	163	-9.8	133.1	-532	499
		SB 207499	334	826.8	150.2	444	1364	334	-9.0	128.6	-582	456
	VISIT 25/WEEK 88	PLACEBO	53	815.0	151.8	566	1132	53	-0.5	147.4	-313	440
		SB 207499	97	825.7	152.8	561	1304	97	-10.4	125.9	-385	326
	VISIT 26/WEEK 92	PLACEBO	52	828.3	166.2	561	1395	52	12.9	147.6	-232	422
		SB 207499	96	822.0	170.3	522	1463	96	-12.6	126.7	-350	263

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.18

DESCRIPTIVE STATISTICS FOR ECGS BY VISIT/WEEK AND PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER	VISIT/WEEK	PRIOR TREATMENT	-----RESULT-----					-----CHANGE FROM BASELINE-----				
			N	MEAN	STD	MIN	MAX	N	MEAN	STD	MIN	MAX
RR (MSEC)	VISIT 27/WEEK 96	PLACEBO	160	820.1	158.0	526	1395	160	-7.8	139.0	-494	401
		SB 207499	328	817.3	146.3	488	1304	328	-20.0	129.0	-524	341
	VISIT 28/WEEK 100	PLACEBO	22	827.0	157.7	536	1111	22	36.6	129.1	-116	499
		SB 207499	49	823.0	157.5	556	1176	49	-1.5	138.4	-354	445
	VISIT 29/WEEK 104	PLACEBO	18	850.9	169.9	541	1132	18	57.9	165.0	-93	479
		SB 207499	40	802.9	155.0	556	1154	40	-6.9	133.5	-354	422
	VISIT 30/WEEK 108	PLACEBO	126	811.9	162.7	488	1333	126	-11.7	140.4	-361	414
		SB 207499	272	820.6	143.4	462	1333	272	-7.1	122.5	-448	340
	VISIT 31/WEEK 112	PLACEBO	9	929.6	120.8	779	1176	9	80.6	167.1	-135	422
		SB 207499	18	789.0	148.6	619	1176	18	21.9	118.4	-138	303
	VISIT 32/WEEK 116	PLACEBO	9	919.1	100.5	779	1053	9	70.0	176.1	-135	440
		SB 207499	16	773.0	143.3	566	1132	16	-5.8	121.4	-284	191
	VISIT 33/WEEK 120	PLACEBO	91	815.0	153.2	550	1333	91	-17.0	145.1	-387	396
		SB 207499	187	806.0	152.8	500	1250	187	-15.0	137.0	-394	494
	VISIT 34/WEEK 124	PLACEBO	3	888.8	165.1	750	1071	3	44.7	72.8	-39	88
		SB 207499	3	734.2	139.2	606	882	3	-57.8	83.5	-119	37
	VISIT 35/WEEK 128	PLACEBO	3	765.7	106.3	674	882	3	-78.4	52.2	-115	-19
		SB 207499	3	724.3	89.8	645	822	3	-67.7	53.8	-127	-23
	VISIT 36/WEEK 132	PLACEBO	36	826.5	153.8	556	1224	36	-7.6	154.0	-319	312
		SB 207499	58	791.1	187.8	517	1714	58	-13.7	153.0	-365	582
	VISIT 37/WEEK 136	PLACEBO	1	779.2	.	779	779	1	-10.2	.	-10	-10
		SB 207499	2	744.8	213.2	594	896	2	-26.6	109.0	-104	51
ENDPOINT		PLACEBO	239	803.4	147.5	472	1333	239	-27.5	132.1	-562	342
		SB 207499	471	809.5	152.9	472	1714	471	-27.2	144.2	-588	582

1. ENDPOINT=LAST VALUE REPORTED ON-THERAPY

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 2/WEEK 1

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN		LOW		NORMAL		HIGH	HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	0
	LOW (50-59 BPM)	24	3 (12.5%)		9 (37.5%)		12 (50.0%)		0	0
	NORMAL (60-99 BPM)	203	0		6 (3.0%)		188 (92.6%)		8 (3.9%)	1 (0.5%)
	HIGH (100-120 BPM)	7	0		0		6 (85.7%)		1 (14.3%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	0	0		0		0		0	0
	TOTAL	234	3 (1.3%)		15 (6.4%)		206 (88.0%)		9 (3.8%)	1 (0.4%)
SB 207499	LOW CONCERN (<50 BPM)	7	2 (28.6%)		2 (28.6%)		3 (42.9%)		0	0
	LOW (50-59 BPM)	59	2 (3.4%)		19 (32.2%)		37 (62.7%)		1 (1.7%)	0
	NORMAL (60-99 BPM)	382	3 (0.8%)		19 (5.0%)		348 (91.1%)		11 (2.9%)	1 (0.3%)
	HIGH (100-120 BPM)	12	0		0		7 (58.3%)		5 (41.7%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	2	0		0		2 (100.0%)		0	0
	TOTAL	462	7 (1.5%)		40 (8.7%)		397 (85.9%)		17 (3.7%)	1 (0.2%)
TOTAL	LOW CONCERN (<50 BPM)	7	2 (28.6%)		2 (28.6%)		3 (42.9%)		0	0
	LOW (50-59 BPM)	83	5 (6.0%)		28 (33.7%)		49 (59.0%)		1 (1.2%)	0
	NORMAL (60-99 BPM)	585	3 (0.5%)		25 (4.3%)		536 (91.6%)		19 (3.2%)	2 (0.3%)
	HIGH (100-120 BPM)	19	0		0		13 (68.4%)		6 (31.6%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	2	0		0		2 (100.0%)		0	0
	TOTAL	696	10 (1.4%)		55 (7.9%)		603 (86.6%)		26 (3.7%)	2 (0.3%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 3/WEEK 2

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN		LOW		NORMAL		HIGH	HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	0
	LOW (50-59 BPM)	24	0		12 (50.0%)		12 (50.0%)		0	0
	NORMAL (60-99 BPM)	192	0		16 (8.3%)		170 (88.5%)		6 (3.1%)	0
	HIGH (100-120 BPM)	7	0		0		6 (85.7%)		1 (14.3%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	0	0		0		0		0	0
	TOTAL	223	0		28 (12.6%)		188 (84.3%)		7 (3.1%)	0
SB 207499	LOW CONCERN (<50 BPM)	7	1 (14.3%)		2 (28.6%)		3 (42.9%)		0	1 (14.3%)
	LOW (50-59 BPM)	57	2 (3.5%)		19 (33.3%)		35 (61.4%)		0	1 (1.8%)
	NORMAL (60-99 BPM)	374	0		27 (7.2%)		339 (90.6%)		8 (2.1%)	0
	HIGH (100-120 BPM)	12	0		0		8 (66.7%)		4 (33.3%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	1	0		0		1 (100.0%)		0	0
	TOTAL	451	3 (0.7%)		48 (10.6%)		386 (85.6%)		12 (2.7%)	2 (0.4%)
TOTAL	LOW CONCERN (<50 BPM)	7	1 (14.3%)		2 (28.6%)		3 (42.9%)		0	1 (14.3%)
	LOW (50-59 BPM)	81	2 (2.5%)		31 (38.3%)		47 (58.0%)		0	1 (1.2%)
	NORMAL (60-99 BPM)	566	0		43 (7.6%)		509 (89.9%)		14 (2.5%)	0
	HIGH (100-120 BPM)	19	0		0		14 (73.7%)		5 (26.3%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	1	0		0		1 (100.0%)		0	0
	TOTAL	674	3 (0.4%)		76 (11.3%)		574 (85.2%)		19 (2.8%)	2 (0.3%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 4/WEEK 4

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN		LOW		NORMAL		HIGH	HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	0
	LOW (50-59 BPM)	23	1 (4.3%)		10 (43.5%)		12 (52.2%)		0	0
	NORMAL (60-99 BPM)	185	0		14 (7.6%)		161 (87.0%)		9 (4.9%)	1 (0.5%)
	HIGH (100-120 BPM)	7	0		0		6 (85.7%)		1 (14.3%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	0	0		0		0		0	0
	TOTAL	215	1 (0.5%)		24 (11.2%)		179 (83.3%)		10 (4.7%)	1 (0.5%)
SB 207499	LOW CONCERN (<50 BPM)	7	1 (14.3%)		4 (57.1%)		2 (28.6%)		0	0
	LOW (50-59 BPM)	58	3 (5.2%)		22 (37.9%)		32 (55.2%)		1 (1.7%)	0
	NORMAL (60-99 BPM)	379	0		22 (5.8%)		343 (90.5%)		13 (3.4%)	1 (0.3%)
	HIGH (100-120 BPM)	12	0		0		8 (66.7%)		4 (33.3%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	2	0		0		2 (100.0%)		0	0
	TOTAL	458	4 (0.9%)		48 (10.5%)		387 (84.5%)		18 (3.9%)	1 (0.2%)
TOTAL	LOW CONCERN (<50 BPM)	7	1 (14.3%)		4 (57.1%)		2 (28.6%)		0	0
	LOW (50-59 BPM)	81	4 (4.9%)		32 (39.5%)		44 (54.3%)		1 (1.2%)	0
	NORMAL (60-99 BPM)	564	0		36 (6.4%)		504 (89.4%)		22 (3.9%)	2 (0.4%)
	HIGH (100-120 BPM)	19	0		0		14 (73.7%)		5 (26.3%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	2	0		0		2 (100.0%)		0	0
	TOTAL	673	5 (0.7%)		72 (10.7%)		566 (84.1%)		28 (4.2%)	2 (0.3%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 5/WEEK 8

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN		LOW		NORMAL		HIGH	HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	
	LOW (50-59 BPM)	23	0		11	(47.8%)	11	(47.8%)	1	(4.3%)
	NORMAL (60-99 BPM)	183	0		12	(6.6%)	161	(88.0%)	9	(4.9%)
	HIGH (100-120 BPM)	7	0		0		6	(85.7%)	1	(14.3%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	
	MISSING	0	0		0		0		0	
	TOTAL	213	0		23	(10.8%)	178	(83.6%)	11	(5.2%)
SB 207499	LOW CONCERN (<50 BPM)	7	2	(28.6%)	2	(28.6%)	3	(42.9%)	0	
	LOW (50-59 BPM)	58	6	(10.3%)	24	(41.4%)	26	(44.8%)	2	(3.4%)
	NORMAL (60-99 BPM)	368	0		19	(5.2%)	340	(92.4%)	7	(1.9%)
	HIGH (100-120 BPM)	12	0		0		7	(58.3%)	5	(41.7%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	
	MISSING	2	0		0		2	(100.0%)	0	
	TOTAL	447	8	(1.8%)	45	(10.1%)	378	(84.6%)	14	(3.1%)
TOTAL	LOW CONCERN (<50 BPM)	7	2	(28.6%)	2	(28.6%)	3	(42.9%)	0	
	LOW (50-59 BPM)	81	6	(7.4%)	35	(43.2%)	37	(45.7%)	3	(3.7%)
	NORMAL (60-99 BPM)	551	0		31	(5.6%)	501	(90.9%)	16	(2.9%)
	HIGH (100-120 BPM)	19	0		0		13	(68.4%)	6	(31.6%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	
	MISSING	2	0		0		2	(100.0%)	0	
	TOTAL	660	8	(1.2%)	68	(10.3%)	556	(84.2%)	25	(3.8%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 6/WEEK 12

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN		LOW		NORMAL		HIGH	HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	0
	LOW (50-59 BPM)	23	1 (4.3%)	12 (52.2%)	8 (34.8%)	2 (8.7%)	0			
	NORMAL (60-99 BPM)	179	0	12 (6.7%)	156 (87.2%)	11 (6.1%)	0			
	HIGH (100-120 BPM)	6	0	0	4 (66.7%)	2 (33.3%)	0			
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0			
	MISSING	0	0	0	0	0	0			
	TOTAL	208	1 (0.5%)	24 (11.5%)	168 (80.8%)	15 (7.2%)	0			
SB 207499	LOW CONCERN (<50 BPM)	7	2 (28.6%)	3 (42.9%)	2 (28.6%)	0		0		
	LOW (50-59 BPM)	55	5 (9.1%)	20 (36.4%)	28 (50.9%)	2 (3.6%)	0			
	NORMAL (60-99 BPM)	368	1 (0.3%)	17 (4.6%)	340 (92.4%)	10 (2.7%)	0			
	HIGH (100-120 BPM)	12	0	0	9 (75.0%)	3 (25.0%)	0			
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0			
	MISSING	2	0	0	2 (100.0%)	0	0			
	TOTAL	444	8 (1.8%)	40 (9.0%)	381 (85.8%)	15 (3.4%)	0			
TOTAL	LOW CONCERN (<50 BPM)	7	2 (28.6%)	3 (42.9%)	2 (28.6%)	0		0		
	LOW (50-59 BPM)	78	6 (7.7%)	32 (41.0%)	36 (46.2%)	4 (5.1%)	0			
	NORMAL (60-99 BPM)	547	1 (0.2%)	29 (5.3%)	496 (90.7%)	21 (3.8%)	0			
	HIGH (100-120 BPM)	18	0	0	13 (72.2%)	5 (27.8%)	0			
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0			
	MISSING	2	0	0	2 (100.0%)	0	0			
	TOTAL	652	9 (1.4%)	64 (9.8%)	549 (84.2%)	30 (4.6%)	0			

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 7/WEEK 16

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN		LOW		NORMAL		HIGH	HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	0
	LOW (50-59 BPM)	23	1 (4.3%)		10 (43.5%)		11 (47.8%)		1 (4.3%)	0
	NORMAL (60-99 BPM)	173	1 (0.6%)		10 (5.8%)		154 (89.0%)		8 (4.6%)	0
	HIGH (100-120 BPM)	6	0		0		4 (66.7%)		2 (33.3%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	0	0		0		0		0	0
	TOTAL	202	2 (1.0%)		20 (9.9%)		169 (83.7%)		11 (5.4%)	0
SB 207499	LOW CONCERN (<50 BPM)	7	1 (14.3%)		5 (71.4%)		0		1 (14.3%)	0
	LOW (50-59 BPM)	53	3 (5.7%)		22 (41.5%)		27 (50.9%)		0	1 (1.9%)
	NORMAL (60-99 BPM)	362	0		18 (5.0%)		330 (91.2%)		12 (3.3%)	2 (0.6%)
	HIGH (100-120 BPM)	12	0		0		7 (58.3%)		5 (41.7%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	2	0		0		1 (50.0%)		1 (50.0%)	0
	TOTAL	436	4 (0.9%)		45 (10.3%)		365 (83.7%)		19 (4.4%)	3 (0.7%)
TOTAL	LOW CONCERN (<50 BPM)	7	1 (14.3%)		5 (71.4%)		0		1 (14.3%)	0
	LOW (50-59 BPM)	76	4 (5.3%)		32 (42.1%)		38 (50.0%)		1 (1.3%)	1 (1.3%)
	NORMAL (60-99 BPM)	535	1 (0.2%)		28 (5.2%)		484 (90.5%)		20 (3.7%)	2 (0.4%)
	HIGH (100-120 BPM)	18	0		0		11 (61.1%)		7 (38.9%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	2	0		0		1 (50.0%)		1 (50.0%)	0
	TOTAL	638	6 (0.9%)		65 (10.2%)		534 (83.7%)		30 (4.7%)	3 (0.5%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 8/WEEK 20

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN		LOW		NORMAL		HIGH	HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	0
	LOW (50-59 BPM)	23	3 (13.0%)		8 (34.8%)		10 (43.5%)		2 (8.7%)	0
	NORMAL (60-99 BPM)	169	0		13 (7.7%)		148 (87.6%)		8 (4.7%)	0
	HIGH (100-120 BPM)	5	0		0		5 (100.0%)		0	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	0	0		0		0		0	0
	TOTAL	197	3 (1.5%)		21 (10.7%)		163 (82.7%)		10 (5.1%)	0
SB 207499	LOW CONCERN (<50 BPM)	7	3 (42.9%)		2 (28.6%)		2 (28.6%)		0	0
	LOW (50-59 BPM)	53	6 (11.3%)		19 (35.8%)		27 (50.9%)		0	1 (1.9%)
	NORMAL (60-99 BPM)	358	0		12 (3.4%)		332 (92.7%)		14 (3.9%)	0
	HIGH (100-120 BPM)	12	0		1 (8.3%)		8 (66.7%)		3 (25.0%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	1	0		0		1 (100.0%)		0	0
	TOTAL	431	9 (2.1%)		34 (7.9%)		370 (85.8%)		17 (3.9%)	1 (0.2%)
TOTAL	LOW CONCERN (<50 BPM)	7	3 (42.9%)		2 (28.6%)		2 (28.6%)		0	0
	LOW (50-59 BPM)	76	9 (11.8%)		27 (35.5%)		37 (48.7%)		2 (2.6%)	1 (1.3%)
	NORMAL (60-99 BPM)	527	0		25 (4.7%)		480 (91.1%)		22 (4.2%)	0
	HIGH (100-120 BPM)	17	0		1 (5.9%)		13 (76.5%)		3 (17.6%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	1	0		0		1 (100.0%)		0	0
	TOTAL	628	12 (1.9%)		55 (8.8%)		533 (84.9%)		27 (4.3%)	1 (0.2%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 9/WEEK 24

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN		LOW		NORMAL		HIGH	HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	0
	LOW (50-59 BPM)	22	1 (4.5%)		9 (40.9%)		10 (45.5%)		2 (9.1%)	0
	NORMAL (60-99 BPM)	166	0		8 (4.8%)		147 (88.6%)		9 (5.4%)	2 (1.2%)
	HIGH (100-120 BPM)	5	0		0		5 (100.0%)		0	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	0	0		0		0		0	0
	TOTAL	193	1 (0.5%)		17 (8.8%)		162 (83.9%)		11 (5.7%)	2 (1.0%)
SB 207499	LOW CONCERN (<50 BPM)	7	1 (14.3%)		4 (57.1%)		2 (28.6%)		0	0
	LOW (50-59 BPM)	52	5 (9.6%)		19 (36.5%)		27 (51.9%)		0	1 (1.9%)
	NORMAL (60-99 BPM)	354	0		18 (5.1%)		319 (90.1%)		16 (4.5%)	1 (0.3%)
	HIGH (100-120 BPM)	12	0		0		9 (75.0%)		2 (16.7%)	1 (8.3%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	2	0		0		2 (100.0%)		0	0
	TOTAL	427	6 (1.4%)		41 (9.6%)		359 (84.1%)		18 (4.2%)	3 (0.7%)
TOTAL	LOW CONCERN (<50 BPM)	7	1 (14.3%)		4 (57.1%)		2 (28.6%)		0	0
	LOW (50-59 BPM)	74	6 (8.1%)		28 (37.8%)		37 (50.0%)		2 (2.7%)	1 (1.4%)
	NORMAL (60-99 BPM)	520	0		26 (5.0%)		466 (89.6%)		25 (4.8%)	3 (0.6%)
	HIGH (100-120 BPM)	17	0		0		14 (82.4%)		2 (11.8%)	1 (5.9%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	2	0		0		2 (100.0%)		0	0
	TOTAL	620	7 (1.1%)		58 (9.4%)		521 (84.0%)		29 (4.7%)	5 (0.8%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 10/WEEK 28

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----								
			LOW CONCERN		LOW		NORMAL		HIGH		HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0		0
	LOW (50-59 BPM)	21	1 (4.8%)		7 (33.3%)		13 (61.9%)		0		0
	NORMAL (60-99 BPM)	164	1 (0.6%)		11 (6.7%)		142 (86.6%)		9 (5.5%)		1 (0.6%)
	HIGH (100-120 BPM)	5	0		0		5 (100.0%)		0		0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	MISSING	0	0		0		0		0		0
	TOTAL	190	2 (1.1%)		18 (9.5%)		160 (84.2%)		9 (4.7%)		1 (0.5%)
SB 207499	LOW CONCERN (<50 BPM)	7	3 (42.9%)		2 (28.6%)		2 (28.6%)		0		0
	LOW (50-59 BPM)	51	2 (3.9%)		20 (39.2%)		28 (54.9%)		0		1 (2.0%)
	NORMAL (60-99 BPM)	350	1 (0.3%)		16 (4.6%)		321 (91.7%)		12 (3.4%)		0
	HIGH (100-120 BPM)	12	0		0		9 (75.0%)		2 (16.7%)		1 (8.3%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	MISSING	2	0		0		2 (100.0%)		0		0
	TOTAL	422	6 (1.4%)		38 (9.0%)		362 (85.8%)		14 (3.3%)		2 (0.5%)
TOTAL	LOW CONCERN (<50 BPM)	7	3 (42.9%)		2 (28.6%)		2 (28.6%)		0		0
	LOW (50-59 BPM)	72	3 (4.2%)		27 (37.5%)		41 (56.9%)		0		1 (1.4%)
	NORMAL (60-99 BPM)	514	2 (0.4%)		27 (5.3%)		463 (90.1%)		21 (4.1%)		1 (0.2%)
	HIGH (100-120 BPM)	17	0		0		14 (82.4%)		2 (11.8%)		1 (5.9%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	MISSING	2	0		0		2 (100.0%)		0		0
	TOTAL	612	8 (1.3%)		56 (9.2%)		522 (85.3%)		23 (3.8%)		3 (0.5%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 11/WEEK 32

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN		LOW		NORMAL		HIGH	HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	0
	LOW (50-59 BPM)	21	1 (4.8%)		9 (42.9%)		10 (47.6%)		1 (4.8%)	0
	NORMAL (60-99 BPM)	160	1 (0.6%)		11 (6.9%)		145 (90.6%)		3 (1.9%)	0
	HIGH (100-120 BPM)	5	0		0		2 (40.0%)		3 (60.0%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	0	0		0		0		0	0
	TOTAL	186	2 (1.1%)		20 (10.8%)		157 (84.4%)		7 (3.8%)	0
SB 207499	LOW CONCERN (<50 BPM)	7	1 (14.3%)		4 (57.1%)		2 (28.6%)		0	0
	LOW (50-59 BPM)	51	4 (7.8%)		18 (35.3%)		27 (52.9%)		1 (2.0%)	1 (2.0%)
	NORMAL (60-99 BPM)	347	0		15 (4.3%)		319 (91.9%)		12 (3.5%)	1 (0.3%)
	HIGH (100-120 BPM)	12	0		0		5 (41.7%)		7 (58.3%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	2	0		0		2 (100.0%)		0	0
	TOTAL	419	5 (1.2%)		37 (8.8%)		355 (84.7%)		20 (4.8%)	2 (0.5%)
TOTAL	LOW CONCERN (<50 BPM)	7	1 (14.3%)		4 (57.1%)		2 (28.6%)		0	0
	LOW (50-59 BPM)	72	5 (6.9%)		27 (37.5%)		37 (51.4%)		2 (2.8%)	1 (1.4%)
	NORMAL (60-99 BPM)	507	1 (0.2%)		26 (5.1%)		464 (91.5%)		15 (3.0%)	1 (0.2%)
	HIGH (100-120 BPM)	17	0		0		7 (41.2%)		10 (58.8%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	2	0		0		2 (100.0%)		0	0
	TOTAL	605	7 (1.2%)		57 (9.4%)		512 (84.6%)		27 (4.5%)	2 (0.3%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 12/WEEK 36

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN		LOW		NORMAL		HIGH	HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	0
	LOW (50-59 BPM)	21	0		9	(42.9%)	10	(47.6%)	2	(9.5%)
	NORMAL (60-99 BPM)	161	0		12	(7.5%)	141	(87.6%)	7	(4.3%)
	HIGH (100-120 BPM)	5	0		0		2	(40.0%)	3	(60.0%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	0	0		0		0		0	0
	TOTAL	187	0		21	(11.2%)	153	(81.8%)	12	(6.4%)
SB 207499	LOW CONCERN (<50 BPM)	7	2	(28.6%)	5	(71.4%)	0		0	0
	LOW (50-59 BPM)	51	3	(5.9%)	18	(35.3%)	29	(56.9%)	0	1 (2.0%)
	NORMAL (60-99 BPM)	339	0		14	(4.1%)	313	(92.3%)	11	(3.2%)
	HIGH (100-120 BPM)	11	0		0		8	(72.7%)	3	(27.3%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	2	0		0		2	(100.0%)	0	0
	TOTAL	410	5	(1.2%)	37	(9.0%)	352	(85.9%)	14	(3.4%)
TOTAL	LOW CONCERN (<50 BPM)	7	2	(28.6%)	5	(71.4%)	0		0	0
	LOW (50-59 BPM)	72	3	(4.2%)	27	(37.5%)	39	(54.2%)	2	(2.8%)
	NORMAL (60-99 BPM)	500	0		26	(5.2%)	454	(90.8%)	18	(3.6%)
	HIGH (100-120 BPM)	16	0		0		10	(62.5%)	6	(37.5%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	2	0		0		2	(100.0%)	0	0
	TOTAL	597	5	(0.8%)	58	(9.7%)	505	(84.6%)	26	(4.4%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 13/WEEK 40

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN		LOW		NORMAL		HIGH	HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	0
	LOW (50-59 BPM)	21	1 (4.8%)		10 (47.6%)		9 (42.9%)		1 (4.8%)	0
	NORMAL (60-99 BPM)	159	0		10 (6.3%)		144 (90.6%)		5 (3.1%)	0
	HIGH (100-120 BPM)	5	0		0		3 (60.0%)		2 (40.0%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	0	0		0		0		0	0
	TOTAL	185	1 (0.5%)		20 (10.8%)		156 (84.3%)		8 (4.3%)	0
SB 207499	LOW CONCERN (<50 BPM)	7	1 (14.3%)		5 (71.4%)		1 (14.3%)		0	0
	LOW (50-59 BPM)	51	3 (5.9%)		22 (43.1%)		25 (49.0%)		0	1 (2.0%)
	NORMAL (60-99 BPM)	333	0		11 (3.3%)		309 (92.8%)		13 (3.9%)	0
	HIGH (100-120 BPM)	11	0		0		9 (81.8%)		2 (18.2%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	2	0		0		2 (100.0%)		0	0
	TOTAL	404	4 (1.0%)		38 (9.4%)		346 (85.6%)		15 (3.7%)	1 (0.2%)
TOTAL	LOW CONCERN (<50 BPM)	7	1 (14.3%)		5 (71.4%)		1 (14.3%)		0	0
	LOW (50-59 BPM)	72	4 (5.6%)		32 (44.4%)		34 (47.2%)		1 (1.4%)	1 (1.4%)
	NORMAL (60-99 BPM)	492	0		21 (4.3%)		453 (92.1%)		18 (3.7%)	0
	HIGH (100-120 BPM)	16	0		0		12 (75.0%)		4 (25.0%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	2	0		0		2 (100.0%)		0	0
	TOTAL	589	5 (0.8%)		58 (9.8%)		502 (85.2%)		23 (3.9%)	1 (0.2%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 14/WEEK 44

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN		LOW		NORMAL		HIGH	HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	
	LOW (50-59 BPM)	20	3 (15.0%)		4 (20.0%)		12 (60.0%)		0	1 (5.0%)
	NORMAL (60-99 BPM)	158	0		16 (10.1%)		133 (84.2%)		9 (5.7%)	0
	HIGH (100-120 BPM)	5	0		0		4 (80.0%)		1 (20.0%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	0	0		0		0		0	0
	TOTAL	183	3 (1.6%)		20 (10.9%)		149 (81.4%)		10 (5.5%)	1 (0.5%)
SB 207499	LOW CONCERN (<50 BPM)	7	2 (28.6%)		5 (71.4%)		0		0	
	LOW (50-59 BPM)	51	2 (3.9%)		16 (31.4%)		31 (60.8%)		0	2 (3.9%)
	NORMAL (60-99 BPM)	333	2 (0.6%)		13 (3.9%)		305 (91.6%)		11 (3.3%)	2 (0.6%)
	HIGH (100-120 BPM)	11	0		1 (9.1%)		8 (72.7%)		2 (18.2%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	2	0		0		2 (100.0%)		0	0
	TOTAL	404	6 (1.5%)		35 (8.7%)		346 (85.6%)		13 (3.2%)	4 (1.0%)
TOTAL	LOW CONCERN (<50 BPM)	7	2 (28.6%)		5 (71.4%)		0		0	
	LOW (50-59 BPM)	71	5 (7.0%)		20 (28.2%)		43 (60.6%)		0	3 (4.2%)
	NORMAL (60-99 BPM)	491	2 (0.4%)		29 (5.9%)		438 (89.2%)		20 (4.1%)	2 (0.4%)
	HIGH (100-120 BPM)	16	0		1 (6.3%)		12 (75.0%)		3 (18.8%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	2	0		0		2 (100.0%)		0	0
	TOTAL	587	9 (1.5%)		55 (9.4%)		495 (84.3%)		23 (3.9%)	5 (0.9%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 15/WEEK 48

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN		LOW		NORMAL		HIGH	HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	0
	LOW (50-59 BPM)	20	1 (5.0%)		8 (40.0%)		11 (55.0%)		0	0
	NORMAL (60-99 BPM)	159	0		12 (7.5%)		133 (83.6%)		13 (8.2%)	1 (0.6%)
	HIGH (100-120 BPM)	5	0		0		4 (80.0%)		1 (20.0%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	0	0		0		0		0	0
	TOTAL	184	1 (0.5%)		20 (10.9%)		148 (80.4%)		14 (7.6%)	1 (0.5%)
SB 207499	LOW CONCERN (<50 BPM)	7	2 (28.6%)		4 (57.1%)		1 (14.3%)		0	0
	LOW (50-59 BPM)	51	2 (3.9%)		21 (41.2%)		28 (54.9%)		0	0
	NORMAL (60-99 BPM)	327	0		22 (6.7%)		290 (88.7%)		14 (4.3%)	1 (0.3%)
	HIGH (100-120 BPM)	11	0		0		9 (81.8%)		2 (18.2%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	2	0		0		2 (100.0%)		0	0
	TOTAL	398	4 (1.0%)		47 (11.8%)		330 (82.9%)		16 (4.0%)	1 (0.3%)
TOTAL	LOW CONCERN (<50 BPM)	7	2 (28.6%)		4 (57.1%)		1 (14.3%)		0	0
	LOW (50-59 BPM)	71	3 (4.2%)		29 (40.8%)		39 (54.9%)		0	0
	NORMAL (60-99 BPM)	486	0		34 (7.0%)		423 (87.0%)		27 (5.6%)	2 (0.4%)
	HIGH (100-120 BPM)	16	0		0		13 (81.3%)		3 (18.8%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	2	0		0		2 (100.0%)		0	0
	TOTAL	582	5 (0.9%)		67 (11.5%)		478 (82.1%)		30 (5.2%)	2 (0.3%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 16/WEEK 52

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----									
			LOW CONCERN		LOW		NORMAL		HIGH	HIGH CONCERN		

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	0		
	LOW (50-59 BPM)	20	2	(10.0%)	7	(35.0%)	11	(55.0%)	0	0		
	NORMAL (60-99 BPM)	156	0		10	(6.4%)	139	(89.1%)	6	(3.8%)		
	HIGH (100-120 BPM)	4	0		0		3	(75.0%)	1	(25.0%)		
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0		
	MISSING	0	0		0		0		0	0		
	TOTAL	180	2	(1.1%)	17	(9.4%)	153	(85.0%)	7	(3.9%)	1	(0.6%)
SB 207499	LOW CONCERN (<50 BPM)	7	0		4	(57.1%)	3	(42.9%)	0	0		
	LOW (50-59 BPM)	47	3	(6.4%)	17	(36.2%)	27	(57.4%)	0	0		
	NORMAL (60-99 BPM)	318	0		16	(5.0%)	291	(91.5%)	11	(3.5%)		
	HIGH (100-120 BPM)	10	0		0		8	(80.0%)	2	(20.0%)		
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0		
	MISSING	2	0		0		2	(100.0%)	0	0		
	TOTAL	384	3	(0.8%)	37	(9.6%)	331	(86.2%)	13	(3.4%)	0	
TOTAL	LOW CONCERN (<50 BPM)	7	0		4	(57.1%)	3	(42.9%)	0	0		
	LOW (50-59 BPM)	67	5	(7.5%)	24	(35.8%)	38	(56.7%)	0	0		
	NORMAL (60-99 BPM)	474	0		26	(5.5%)	430	(90.7%)	17	(3.6%)	1	(0.2%)
	HIGH (100-120 BPM)	14	0		0		11	(78.6%)	3	(21.4%)	0	
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0		
	MISSING	2	0		0		2	(100.0%)	0	0		
	TOTAL	564	5	(0.9%)	54	(9.6%)	484	(85.8%)	20	(3.5%)	1	(0.2%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 17/WEEK 56

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN		LOW		NORMAL		HIGH	HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	
	LOW (50-59 BPM)	19	3 (15.8%)		6 (31.6%)		10 (52.6%)		0	0
	NORMAL (60-99 BPM)	147	0		9 (6.1%)		128 (87.1%)		10 (6.8%)	0
	HIGH (100-120 BPM)	3	0		0		2 (66.7%)		1 (33.3%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	0	0		0		0		0	0
	TOTAL	169	3 (1.8%)		15 (8.9%)		140 (82.8%)		11 (6.5%)	0
SB 207499	LOW CONCERN (<50 BPM)	6	2 (33.3%)		2 (33.3%)		2 (33.3%)		0	0
	LOW (50-59 BPM)	45	2 (4.4%)		15 (33.3%)		27 (60.0%)		0	1 (2.2%)
	NORMAL (60-99 BPM)	301	0		16 (5.3%)		269 (89.4%)		14 (4.7%)	2 (0.7%)
	HIGH (100-120 BPM)	10	0		0		7 (70.0%)		3 (30.0%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	2	0		0		2 (100.0%)		0	0
	TOTAL	364	4 (1.1%)		33 (9.1%)		307 (84.3%)		17 (4.7%)	3 (0.8%)
TOTAL	LOW CONCERN (<50 BPM)	6	2 (33.3%)		2 (33.3%)		2 (33.3%)		0	0
	LOW (50-59 BPM)	64	5 (7.8%)		21 (32.8%)		37 (57.8%)		0	1 (1.6%)
	NORMAL (60-99 BPM)	448	0		25 (5.6%)		397 (88.6%)		24 (5.4%)	2 (0.4%)
	HIGH (100-120 BPM)	13	0		0		9 (69.2%)		4 (30.8%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	2	0		0		2 (100.0%)		0	0
	TOTAL	533	7 (1.3%)		48 (9.0%)		447 (83.9%)		28 (5.3%)	3 (0.6%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 18/WEEK 60

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN		LOW		NORMAL		HIGH	HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	0
	LOW (50-59 BPM)	19	1 (5.3%)		6 (31.6%)		12 (63.2%)		0	0
	NORMAL (60-99 BPM)	150	0		15 (10.0%)		124 (82.7%)		9 (6.0%)	2 (1.3%)
	HIGH (100-120 BPM)	4	0		0		2 (50.0%)		2 (50.0%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	0	0		0		0		0	0
	TOTAL	173	1 (0.6%)		21 (12.1%)		138 (79.8%)		11 (6.4%)	2 (1.2%)
SB 207499	LOW CONCERN (<50 BPM)	6	1 (16.7%)		2 (33.3%)		3 (50.0%)		0	0
	LOW (50-59 BPM)	47	2 (4.3%)		10 (21.3%)		33 (70.2%)		1 (2.1%)	1 (2.1%)
	NORMAL (60-99 BPM)	309	0		15 (4.9%)		278 (90.0%)		15 (4.9%)	1 (0.3%)
	HIGH (100-120 BPM)	10	0		0		8 (80.0%)		1 (10.0%)	1 (10.0%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	2	0		0		1 (50.0%)		1 (50.0%)	0
	TOTAL	374	3 (0.8%)		27 (7.2%)		323 (86.4%)		18 (4.8%)	3 (0.8%)
TOTAL	LOW CONCERN (<50 BPM)	6	1 (16.7%)		2 (33.3%)		3 (50.0%)		0	0
	LOW (50-59 BPM)	66	3 (4.5%)		16 (24.2%)		45 (68.2%)		1 (1.5%)	1 (1.5%)
	NORMAL (60-99 BPM)	459	0		30 (6.5%)		402 (87.6%)		24 (5.2%)	3 (0.7%)
	HIGH (100-120 BPM)	14	0		0		10 (71.4%)		3 (21.4%)	1 (7.1%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	2	0		0		1 (50.0%)		1 (50.0%)	0
	TOTAL	547	4 (0.7%)		48 (8.8%)		461 (84.3%)		29 (5.3%)	5 (0.9%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 19/WEEK 64

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN		LOW		NORMAL		HIGH	HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	0
	LOW (50-59 BPM)	15	2 (13.3%)		5 (33.3%)		8 (53.3%)		0	0
	NORMAL (60-99 BPM)	125	0		9 (7.2%)		110 (88.0%)		6 (4.8%)	0
	HIGH (100-120 BPM)	2	0		0		2 (100.0%)		0	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	0	0		0		0		0	0
	TOTAL	142	2 (1.4%)		14 (9.9%)		120 (84.5%)		6 (4.2%)	0
SB 207499	LOW CONCERN (<50 BPM)	4	3 (75.0%)		1 (25.0%)		0		0	0
	LOW (50-59 BPM)	32	1 (3.1%)		8 (25.0%)		22 (68.8%)		1 (3.1%)	0
	NORMAL (60-99 BPM)	261	1 (0.4%)		9 (3.4%)		235 (90.0%)		13 (5.0%)	3 (1.1%)
	HIGH (100-120 BPM)	9	0		0		5 (55.6%)		4 (44.4%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	2	0		0		2 (100.0%)		0	0
	TOTAL	308	5 (1.6%)		18 (5.8%)		264 (85.7%)		18 (5.8%)	3 (1.0%)
TOTAL	LOW CONCERN (<50 BPM)	4	3 (75.0%)		1 (25.0%)		0		0	0
	LOW (50-59 BPM)	47	3 (6.4%)		13 (27.7%)		30 (63.8%)		1 (2.1%)	0
	NORMAL (60-99 BPM)	386	1 (0.3%)		18 (4.7%)		345 (89.4%)		19 (4.9%)	3 (0.8%)
	HIGH (100-120 BPM)	11	0		0		7 (63.6%)		4 (36.4%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	2	0		0		2 (100.0%)		0	0
	TOTAL	450	7 (1.6%)		32 (7.1%)		384 (85.3%)		24 (5.3%)	3 (0.7%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 20/WEEK 68

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN		LOW		NORMAL		HIGH	HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	0
	LOW (50-59 BPM)	15	2 (13.3%)		6 (40.0%)		7 (46.7%)		0	0
	NORMAL (60-99 BPM)	123	0		5 (4.1%)		112 (91.1%)		6 (4.9%)	0
	HIGH (100-120 BPM)	2	0		0		1 (50.0%)		1 (50.0%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	0	0		0		0		0	0
	TOTAL	140	2 (1.4%)		11 (7.9%)		120 (85.7%)		7 (5.0%)	0
SB 207499	LOW CONCERN (<50 BPM)	4	1 (25.0%)		2 (50.0%)		1 (25.0%)		0	0
	LOW (50-59 BPM)	29	1 (3.4%)		9 (31.0%)		19 (65.5%)		0	0
	NORMAL (60-99 BPM)	251	0		13 (5.2%)		227 (90.4%)		10 (4.0%)	1 (0.4%)
	HIGH (100-120 BPM)	9	0		0		7 (77.8%)		2 (22.2%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	2	0		0		1 (50.0%)		1 (50.0%)	0
	TOTAL	295	2 (0.7%)		24 (8.1%)		255 (86.4%)		13 (4.4%)	1 (0.3%)
TOTAL	LOW CONCERN (<50 BPM)	4	1 (25.0%)		2 (50.0%)		1 (25.0%)		0	0
	LOW (50-59 BPM)	44	3 (6.8%)		15 (34.1%)		26 (59.1%)		0	0
	NORMAL (60-99 BPM)	374	0		18 (4.8%)		339 (90.6%)		16 (4.3%)	1 (0.3%)
	HIGH (100-120 BPM)	11	0		0		8 (72.7%)		3 (27.3%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	2	0		0		1 (50.0%)		1 (50.0%)	0
	TOTAL	435	4 (0.9%)		35 (8.0%)		375 (86.2%)		20 (4.6%)	1 (0.2%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 21/WEEK 72

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN		LOW		NORMAL		HIGH	HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	
	LOW (50-59 BPM)	19	2	(10.5%)	6	(31.6%)	10	(52.6%)	1	(5.3%)
	NORMAL (60-99 BPM)	147	0		11	(7.5%)	129	(87.8%)	7	(4.8%)
	HIGH (100-120 BPM)	4	0		0		4	(100.0%)	0	
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	
	MISSING	0	0		0		0		0	
	TOTAL	170	2	(1.2%)	17	(10.0%)	143	(84.1%)	8	(4.7%)
SB 207499	LOW CONCERN (<50 BPM)	6	3	(50.0%)	2	(33.3%)	1	(16.7%)	0	
	LOW (50-59 BPM)	46	2	(4.3%)	20	(43.5%)	22	(47.8%)	1	(2.2%)
	NORMAL (60-99 BPM)	293	2	(0.7%)	16	(5.5%)	262	(89.4%)	12	(4.1%)
	HIGH (100-120 BPM)	10	0		0		5	(50.0%)	4	(40.0%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	
	MISSING	2	0		0		2	(100.0%)	0	
	TOTAL	357	7	(2.0%)	38	(10.6%)	292	(81.8%)	17	(4.8%)
TOTAL	LOW CONCERN (<50 BPM)	6	3	(50.0%)	2	(33.3%)	1	(16.7%)	0	
	LOW (50-59 BPM)	65	4	(6.2%)	26	(40.0%)	32	(49.2%)	2	(3.1%)
	NORMAL (60-99 BPM)	440	2	(0.5%)	27	(6.1%)	391	(88.9%)	19	(4.3%)
	HIGH (100-120 BPM)	14	0		0		9	(64.3%)	4	(28.6%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	
	MISSING	2	0		0		2	(100.0%)	0	
	TOTAL	527	9	(1.7%)	55	(10.4%)	435	(82.5%)	25	(4.7%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 22/WEEK 76

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN	LOW	NORMAL		HIGH	HIGH CONCERN		

PLACEBO	LOW CONCERN (<50 BPM)	0	0	0	0	0	0	0		
	LOW (50-59 BPM)	12	0	4 (33.3%)	8 (66.7%)	0	0	0		
	NORMAL (60-99 BPM)	86	0	5 (5.8%)	73 (84.9%)	6 (7.0%)	2 (2.3%)			
	HIGH (100-120 BPM)	2	0	0	1 (50.0%)	1 (50.0%)	0			
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0			
	MISSING	0	0	0	0	0	0			
	TOTAL	100	0	9 (9.0%)	82 (82.0%)	7 (7.0%)	2 (2.0%)			
SB 207499	LOW CONCERN (<50 BPM)	3	0	2 (66.7%)	0	1 (33.3%)	0			
	LOW (50-59 BPM)	18	0	9 (50.0%)	9 (50.0%)	0	0			
	NORMAL (60-99 BPM)	169	0	6 (3.6%)	156 (92.3%)	6 (3.6%)	1 (0.6%)			
	HIGH (100-120 BPM)	6	0	0	4 (66.7%)	2 (33.3%)	0			
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0			
	MISSING	2	0	0	2 (100.0%)	0	0			
	TOTAL	198	0	17 (8.6%)	171 (86.4%)	9 (4.5%)	1 (0.5%)			
TOTAL	LOW CONCERN (<50 BPM)	3	0	2 (66.7%)	0	1 (33.3%)	0			
	LOW (50-59 BPM)	30	0	13 (43.3%)	17 (56.7%)	0	0			
	NORMAL (60-99 BPM)	255	0	11 (4.3%)	229 (89.8%)	12 (4.7%)	3 (1.2%)			
	HIGH (100-120 BPM)	8	0	0	5 (62.5%)	3 (37.5%)	0			
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0			
	MISSING	2	0	0	2 (100.0%)	0	0			
	TOTAL	298	0	26 (8.7%)	253 (84.9%)	16 (5.4%)	3 (1.0%)			

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 23/WEEK 80

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN		LOW		NORMAL		HIGH	HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	0
	LOW (50-59 BPM)	12	2 (16.7%)		4 (33.3%)		6 (50.0%)		0	0
	NORMAL (60-99 BPM)	84	0		3 (3.6%)		74 (88.1%)		7 (8.3%)	0
	HIGH (100-120 BPM)	2	0		0		1 (50.0%)		1 (50.0%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	0	0		0		0		0	0
	TOTAL	98	2 (2.0%)		7 (7.1%)		81 (82.7%)		8 (8.2%)	0
SB 207499	LOW CONCERN (<50 BPM)	3	2 (66.7%)		1 (33.3%)		0		0	0
	LOW (50-59 BPM)	17	1 (5.9%)		5 (29.4%)		11 (64.7%)		0	0
	NORMAL (60-99 BPM)	165	1 (0.6%)		10 (6.1%)		147 (89.1%)		6 (3.6%)	1 (0.6%)
	HIGH (100-120 BPM)	6	0		0		5 (83.3%)		1 (16.7%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	2	0		0		2 (100.0%)		0	0
	TOTAL	193	4 (2.1%)		16 (8.3%)		165 (85.5%)		7 (3.6%)	1 (0.5%)
TOTAL	LOW CONCERN (<50 BPM)	3	2 (66.7%)		1 (33.3%)		0		0	0
	LOW (50-59 BPM)	29	3 (10.3%)		9 (31.0%)		17 (58.6%)		0	0
	NORMAL (60-99 BPM)	249	1 (0.4%)		13 (5.2%)		221 (88.8%)		13 (5.2%)	1 (0.4%)
	HIGH (100-120 BPM)	8	0		0		6 (75.0%)		2 (25.0%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	2	0		0		2 (100.0%)		0	0
	TOTAL	291	6 (2.1%)		23 (7.9%)		246 (84.5%)		15 (5.2%)	1 (0.3%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 24/WEEK 84

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN		LOW		NORMAL		HIGH	HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	0
	LOW (50-59 BPM)	18	1 (5.6%)		10 (55.6%)		6 (33.3%)		1 (5.6%)	0
	NORMAL (60-99 BPM)	141	0		9 (6.4%)		121 (85.8%)		11 (7.8%)	0
	HIGH (100-120 BPM)	4	0		0		3 (75.0%)		1 (25.0%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	0	0		0		0		0	0
	TOTAL	163	1 (0.6%)		19 (11.7%)		130 (79.8%)		13 (8.0%)	0
SB 207499	LOW CONCERN (<50 BPM)	5	2 (40.0%)		2 (40.0%)		1 (20.0%)		0	0
	LOW (50-59 BPM)	44	5 (11.4%)		10 (22.7%)		28 (63.6%)		1 (2.3%)	0
	NORMAL (60-99 BPM)	273	1 (0.4%)		14 (5.1%)		246 (90.1%)		11 (4.0%)	1 (0.4%)
	HIGH (100-120 BPM)	10	0		1 (10.0%)		7 (70.0%)		2 (20.0%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	2	0		0		2 (100.0%)		0	0
	TOTAL	334	8 (2.4%)		27 (8.1%)		284 (85.0%)		14 (4.2%)	1 (0.3%)
TOTAL	LOW CONCERN (<50 BPM)	5	2 (40.0%)		2 (40.0%)		1 (20.0%)		0	0
	LOW (50-59 BPM)	62	6 (9.7%)		20 (32.3%)		34 (54.8%)		2 (3.2%)	0
	NORMAL (60-99 BPM)	414	1 (0.2%)		23 (5.6%)		367 (88.6%)		22 (5.3%)	1 (0.2%)
	HIGH (100-120 BPM)	14	0		1 (7.1%)		10 (71.4%)		3 (21.4%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	2	0		0		2 (100.0%)		0	0
	TOTAL	497	9 (1.8%)		46 (9.3%)		414 (83.3%)		27 (5.4%)	1 (0.2%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 25/WEEK 88

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----								
			LOW CONCERN		LOW		NORMAL		HIGH		HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0		0
	LOW (50-59 BPM)	5	0		2	(40.0%)	3	(60.0%)	0		0
	NORMAL (60-99 BPM)	46	0		6	(13.0%)	37	(80.4%)	3	(6.5%)	0
	HIGH (100-120 BPM)	2	0		0		1	(50.0%)	1	(50.0%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	MISSING	0	0		0		0		0		0
	TOTAL	53	0		8	(15.1%)	41	(77.4%)	4	(7.5%)	0
SB 207499	LOW CONCERN (<50 BPM)	2	1	(50.0%)	1	(50.0%)	0		0		0
	LOW (50-59 BPM)	12	0		6	(50.0%)	6	(50.0%)	0		0
	NORMAL (60-99 BPM)	80	0		3	(3.8%)	71	(88.8%)	5	(6.3%)	1 (1.3%)
	HIGH (100-120 BPM)	3	0		0		2	(66.7%)	1	(33.3%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	MISSING	0	0		0		0		0		0
	TOTAL	97	1	(1.0%)	10	(10.3%)	79	(81.4%)	6	(6.2%)	1 (1.0%)
TOTAL	LOW CONCERN (<50 BPM)	2	1	(50.0%)	1	(50.0%)	0		0		0
	LOW (50-59 BPM)	17	0		8	(47.1%)	9	(52.9%)	0		0
	NORMAL (60-99 BPM)	126	0		9	(7.1%)	108	(85.7%)	8	(6.3%)	1 (0.8%)
	HIGH (100-120 BPM)	5	0		0		3	(60.0%)	2	(40.0%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	MISSING	0	0		0		0		0		0
	TOTAL	150	1	(0.7%)	18	(12.0%)	120	(80.0%)	10	(6.7%)	1 (0.7%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 26/WEEK 92

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN		LOW		NORMAL		HIGH	HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	
	LOW (50-59 BPM)	5	1 (20.0%)		1 (20.0%)		3 (60.0%)		0	
	NORMAL (60-99 BPM)	45	0		6 (13.3%)		34 (75.6%)		5 (11.1%)	
	HIGH (100-120 BPM)	2	0		0		2 (100.0%)		0	
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	
	MISSING	0	0		0		0		0	
	TOTAL	52	1 (1.9%)		7 (13.5%)		39 (75.0%)		5 (9.6%)	
SB 207499	LOW CONCERN (<50 BPM)	2	2 (100.0%)		0		0		0	
	LOW (50-59 BPM)	12	0		6 (50.0%)		6 (50.0%)		0	
	NORMAL (60-99 BPM)	79	0		3 (3.8%)		69 (87.3%)		6 (7.6%)	1 (1.3%)
	HIGH (100-120 BPM)	3	0		0		2 (66.7%)		1 (33.3%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	
	MISSING	0	0		0		0		0	
	TOTAL	96	2 (2.1%)		9 (9.4%)		77 (80.2%)		7 (7.3%)	1 (1.0%)
TOTAL	LOW CONCERN (<50 BPM)	2	2 (100.0%)		0		0		0	
	LOW (50-59 BPM)	17	1 (5.9%)		7 (41.2%)		9 (52.9%)		0	
	NORMAL (60-99 BPM)	124	0		9 (7.3%)		103 (83.1%)		11 (8.9%)	1 (0.8%)
	HIGH (100-120 BPM)	5	0		0		4 (80.0%)		1 (20.0%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	
	MISSING	0	0		0		0		0	
	TOTAL	148	3 (2.0%)		16 (10.8%)		116 (78.4%)		12 (8.1%)	1 (0.7%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 27/WEEK 96

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN		LOW		NORMAL		HIGH	HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	0
	LOW (50-59 BPM)	19	4 (21.1%)		6 (31.6%)		9 (47.4%)		0	0
	NORMAL (60-99 BPM)	137	0		10 (7.3%)		120 (87.6%)		7 (5.1%)	0
	HIGH (100-120 BPM)	4	0		0		3 (75.0%)		1 (25.0%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	0	0		0		0		0	0
	TOTAL	160	4 (2.5%)		16 (10.0%)		132 (82.5%)		8 (5.0%)	0
SB 207499	LOW CONCERN (<50 BPM)	6	2 (33.3%)		4 (66.7%)		0		0	0
	LOW (50-59 BPM)	44	1 (2.3%)		13 (29.5%)		29 (65.9%)		0	1 (2.3%)
	NORMAL (60-99 BPM)	267	0		13 (4.9%)		241 (90.3%)		10 (3.7%)	3 (1.1%)
	HIGH (100-120 BPM)	9	0		0		6 (66.7%)		3 (33.3%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	2	0		0		2 (100.0%)		0	0
	TOTAL	328	3 (0.9%)		30 (9.1%)		278 (84.8%)		13 (4.0%)	4 (1.2%)
TOTAL	LOW CONCERN (<50 BPM)	6	2 (33.3%)		4 (66.7%)		0		0	0
	LOW (50-59 BPM)	63	5 (7.9%)		19 (30.2%)		38 (60.3%)		0	1 (1.6%)
	NORMAL (60-99 BPM)	404	0		23 (5.7%)		361 (89.4%)		17 (4.2%)	3 (0.7%)
	HIGH (100-120 BPM)	13	0		0		9 (69.2%)		4 (30.8%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	2	0		0		2 (100.0%)		0	0
	TOTAL	488	7 (1.4%)		46 (9.4%)		410 (84.0%)		21 (4.3%)	4 (0.8%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 28/WEEK 100

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN	
PLACEBO	LOW CONCERN (<50 BPM)	0	0	0	0	0	0	
	LOW (50-59 BPM)	1	0	1 (100.0%)	0	0	0	
	NORMAL (60-99 BPM)	21	0	2 (9.5%)	18 (85.7%)	1 (4.8%)	0	
	HIGH (100-120 BPM)	0	0	0	0	0	0	
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0	
	MISSING	0	0	0	0	0	0	
	TOTAL	22	0	3 (13.6%)	18 (81.8%)	1 (4.5%)	0	
SB 207499	LOW CONCERN (<50 BPM)	1	0	0	1 (100.0%)	0	0	
	LOW (50-59 BPM)	6	0	3 (50.0%)	3 (50.0%)	0	0	
	NORMAL (60-99 BPM)	40	0	3 (7.5%)	35 (87.5%)	1 (2.5%)	1 (2.5%)	
	HIGH (100-120 BPM)	1	0	0	1 (100.0%)	0	0	
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0	
	MISSING	1	0	0	1 (100.0%)	0	0	
	TOTAL	49	0	6 (12.2%)	41 (83.7%)	1 (2.0%)	1 (2.0%)	
TOTAL	LOW CONCERN (<50 BPM)	1	0	0	1 (100.0%)	0	0	
	LOW (50-59 BPM)	7	0	4 (57.1%)	3 (42.9%)	0	0	
	NORMAL (60-99 BPM)	61	0	5 (8.2%)	53 (86.9%)	2 (3.3%)	1 (1.6%)	
	HIGH (100-120 BPM)	1	0	0	1 (100.0%)	0	0	
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0	
	MISSING	1	0	0	1 (100.0%)	0	0	
	TOTAL	71	0	9 (12.7%)	59 (83.1%)	2 (2.8%)	1 (1.4%)	

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 29/WEEK 104

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN	
PLACEBO	LOW CONCERN (<50 BPM)	0	0	0	0	0	0	0
	LOW (50-59 BPM)	1	0	0	1 (100.0%)	0	0	0
	NORMAL (60-99 BPM)	17	0	3 (17.6%)	12 (70.6%)	2 (11.8%)	0	0
	HIGH (100-120 BPM)	0	0	0	0	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0	0
	MISSING	0	0	0	0	0	0	0
	TOTAL	18	0	3 (16.7%)	13 (72.2%)	2 (11.1%)	0	0
SB 207499	LOW CONCERN (<50 BPM)	0	0	0	0	0	0	0
	LOW (50-59 BPM)	4	0	2 (50.0%)	2 (50.0%)	0	0	0
	NORMAL (60-99 BPM)	34	0	3 (8.8%)	29 (85.3%)	2 (5.9%)	0	0
	HIGH (100-120 BPM)	1	0	0	1 (100.0%)	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0	0
	MISSING	0	0	0	0	0	0	0
	TOTAL	39	0	5 (12.8%)	32 (82.1%)	2 (5.1%)	0	0
TOTAL	LOW CONCERN (<50 BPM)	0	0	0	0	0	0	0
	LOW (50-59 BPM)	5	0	2 (40.0%)	3 (60.0%)	0	0	0
	NORMAL (60-99 BPM)	51	0	6 (11.8%)	41 (80.4%)	4 (7.8%)	0	0
	HIGH (100-120 BPM)	1	0	0	1 (100.0%)	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0	0
	MISSING	0	0	0	0	0	0	0
	TOTAL	57	0	8 (14.0%)	45 (78.9%)	4 (7.0%)	0	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 30/WEEK 108

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN		LOW		NORMAL		HIGH	HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	
	LOW (50-59 BPM)	13	3 (23.1%)		5 (38.5%)		5 (38.5%)		0	0
	NORMAL (60-99 BPM)	112	0		6 (5.4%)		96 (85.7%)		9 (8.0%)	1 (0.9%)
	HIGH (100-120 BPM)	1	0		0		1 (100.0%)		0	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	0	0		0		0		0	0
	TOTAL	126	3 (2.4%)		11 (8.7%)		102 (81.0%)		9 (7.1%)	1 (0.8%)
SB 207499	LOW CONCERN (<50 BPM)	3	0		3 (100.0%)		0		0	0
	LOW (50-59 BPM)	36	1 (2.8%)		13 (36.1%)		22 (61.1%)		0	0
	NORMAL (60-99 BPM)	224	0		9 (4.0%)		200 (89.3%)		14 (6.3%)	1 (0.4%)
	HIGH (100-120 BPM)	8	0		0		7 (87.5%)		0	1 (12.5%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	1	0		0		1 (100.0%)		0	0
	TOTAL	272	1 (0.4%)		25 (9.2%)		230 (84.6%)		14 (5.1%)	2 (0.7%)
TOTAL	LOW CONCERN (<50 BPM)	3	0		3 (100.0%)		0		0	0
	LOW (50-59 BPM)	49	4 (8.2%)		18 (36.7%)		27 (55.1%)		0	0
	NORMAL (60-99 BPM)	336	0		15 (4.5%)		296 (88.1%)		23 (6.8%)	2 (0.6%)
	HIGH (100-120 BPM)	9	0		0		8 (88.9%)		0	1 (11.1%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	MISSING	1	0		0		1 (100.0%)		0	0
	TOTAL	398	4 (1.0%)		36 (9.0%)		332 (83.4%)		23 (5.8%)	3 (0.8%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 31/WEEK 112

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<50 BPM)	0	0	0	0	0	0
	LOW (50-59 BPM)	1	0	0	1 (100.0%)	0	0
	NORMAL (60-99 BPM)	8	0	2 (25.0%)	6 (75.0%)	0	0
	HIGH (100-120 BPM)	0	0	0	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	MISSING	0	0	0	0	0	0
	TOTAL	9	0	2 (22.2%)	7 (77.8%)	0	0
SB 207499	LOW CONCERN (<50 BPM)	0	0	0	0	0	0
	LOW (50-59 BPM)	1	0	1 (100.0%)	0	0	0
	NORMAL (60-99 BPM)	16	0	1 (6.3%)	15 (93.8%)	0	0
	HIGH (100-120 BPM)	1	0	0	1 (100.0%)	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	MISSING	0	0	0	0	0	0
	TOTAL	18	0	2 (11.1%)	16 (88.9%)	0	0
TOTAL	LOW CONCERN (<50 BPM)	0	0	0	0	0	0
	LOW (50-59 BPM)	2	0	1 (50.0%)	1 (50.0%)	0	0
	NORMAL (60-99 BPM)	24	0	3 (12.5%)	21 (87.5%)	0	0
	HIGH (100-120 BPM)	1	0	0	1 (100.0%)	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	MISSING	0	0	0	0	0	0
	TOTAL	27	0	4 (14.8%)	23 (85.2%)	0	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 32/WEEK 116

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN	
PLACEBO	LOW CONCERN (<50 BPM)	0	0	0	0	0	0	
	LOW (50-59 BPM)	1	0	0	1 (100.0%)	0	0	
	NORMAL (60-99 BPM)	8	0	1 (12.5%)	7 (87.5%)	0	0	
	HIGH (100-120 BPM)	0	0	0	0	0	0	
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0	
	MISSING	0	0	0	0	0	0	
	TOTAL	9	0	1 (11.1%)	8 (88.9%)	0	0	
SB 207499	LOW CONCERN (<50 BPM)	0	0	0	0	0	0	
	LOW (50-59 BPM)	1	0	1 (100.0%)	0	0	0	
	NORMAL (60-99 BPM)	15	0	0	12 (80.0%)	2 (13.3%)	1 (6.7%)	
	HIGH (100-120 BPM)	0	0	0	0	0	0	
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0	
	MISSING	0	0	0	0	0	0	
	TOTAL	16	0	1 (6.3%)	12 (75.0%)	2 (12.5%)	1 (6.3%)	
TOTAL	LOW CONCERN (<50 BPM)	0	0	0	0	0	0	
	LOW (50-59 BPM)	2	0	1 (50.0%)	1 (50.0%)	0	0	
	NORMAL (60-99 BPM)	23	0	1 (4.3%)	19 (82.6%)	2 (8.7%)	1 (4.3%)	
	HIGH (100-120 BPM)	0	0	0	0	0	0	
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0	
	MISSING	0	0	0	0	0	0	
	TOTAL	25	0	2 (8.0%)	20 (80.0%)	2 (8.0%)	1 (4.0%)	

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 33/WEEK 120

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN	LOW	NORMAL		HIGH	HIGH CONCERN		
PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	
	LOW (50-59 BPM)	11	1 (9.1%)	5 (45.5%)	5 (45.5%)	0		0		
	NORMAL (60-99 BPM)	80	1 (1.3%)	2 (2.5%)	71 (88.8%)	6 (7.5%)		0		
	HIGH (100-120 BPM)	0	0	0	0	0		0		
	HIGH CONCERN (>120 BPM)	0	0	0	0	0		0		
	MISSING	0	0	0	0	0		0		
	TOTAL	91	2 (2.2%)	7 (7.7%)	76 (83.5%)	6 (6.6%)		0		
SB 207499	LOW CONCERN (<50 BPM)	3	1 (33.3%)	1 (33.3%)	1 (33.3%)	0		0		
	LOW (50-59 BPM)	21	0	8 (38.1%)	13 (61.9%)	0		0		
	NORMAL (60-99 BPM)	158	0	11 (7.0%)	137 (86.7%)	10 (6.3%)		0		
	HIGH (100-120 BPM)	5	0	0	4 (80.0%)	1 (20.0%)		0		
	HIGH CONCERN (>120 BPM)	0	0	0	0	0		0		
	MISSING	0	0	0	0	0		0		
	TOTAL	187	1 (0.5%)	20 (10.7%)	155 (82.9%)	11 (5.9%)		0		
TOTAL	LOW CONCERN (<50 BPM)	3	1 (33.3%)	1 (33.3%)	1 (33.3%)	0		0		
	LOW (50-59 BPM)	32	1 (3.1%)	13 (40.6%)	18 (56.3%)	0		0		
	NORMAL (60-99 BPM)	238	1 (0.4%)	13 (5.5%)	208 (87.4%)	16 (6.7%)		0		
	HIGH (100-120 BPM)	5	0	0	4 (80.0%)	1 (20.0%)		0		
	HIGH CONCERN (>120 BPM)	0	0	0	0	0		0		
	MISSING	0	0	0	0	0		0		
	TOTAL	278	3 (1.1%)	27 (9.7%)	231 (83.1%)	17 (6.1%)		0		

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 34/WEEK 124

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<50 BPM)	0	0	0	0	0	0
	LOW (50-59 BPM)	0	0	0	0	0	0
	NORMAL (60-99 BPM)	3	0	1 (33.3%)	2 (66.7%)	0	0
	HIGH (100-120 BPM)	0	0	0	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	MISSING	0	0	0	0	0	0
	TOTAL	3	0	1 (33.3%)	2 (66.7%)	0	0
SB 207499	LOW CONCERN (<50 BPM)	0	0	0	0	0	0
	LOW (50-59 BPM)	0	0	0	0	0	0
	NORMAL (60-99 BPM)	3	0	0	3 (100.0%)	0	0
	HIGH (100-120 BPM)	0	0	0	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	MISSING	0	0	0	0	0	0
	TOTAL	3	0	0	3 (100.0%)	0	0
TOTAL	LOW CONCERN (<50 BPM)	0	0	0	0	0	0
	LOW (50-59 BPM)	0	0	0	0	0	0
	NORMAL (60-99 BPM)	6	0	1 (16.7%)	5 (83.3%)	0	0
	HIGH (100-120 BPM)	0	0	0	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	MISSING	0	0	0	0	0	0
	TOTAL	6	0	1 (16.7%)	5 (83.3%)	0	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 35/WEEK 128

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<50 BPM)	0	0	0	0	0	0
	LOW (50-59 BPM)	0	0	0	0	0	0
	NORMAL (60-99 BPM)	3	0	0	3 (100.0%)	0	0
	HIGH (100-120 BPM)	0	0	0	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	MISSING	0	0	0	0	0	0
	TOTAL	3	0	0	3 (100.0%)	0	0
SB 207499	LOW CONCERN (<50 BPM)	0	0	0	0	0	0
	LOW (50-59 BPM)	0	0	0	0	0	0
	NORMAL (60-99 BPM)	3	0	0	3 (100.0%)	0	0
	HIGH (100-120 BPM)	0	0	0	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	MISSING	0	0	0	0	0	0
	TOTAL	3	0	0	3 (100.0%)	0	0
TOTAL	LOW CONCERN (<50 BPM)	0	0	0	0	0	0
	LOW (50-59 BPM)	0	0	0	0	0	0
	NORMAL (60-99 BPM)	6	0	0	6 (100.0%)	0	0
	HIGH (100-120 BPM)	0	0	0	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	MISSING	0	0	0	0	0	0
	TOTAL	6	0	0	6 (100.0%)	0	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 36/WEEK 132

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN	
PLACEBO	LOW CONCERN (<50 BPM)	0	0	0	0	0	0	0
	LOW (50-59 BPM)	6	1 (16.7%)	1 (16.7%)	4 (66.7%)	0	0	0
	NORMAL (60-99 BPM)	30	0	3 (10.0%)	25 (83.3%)	2 (6.7%)	0	0
	HIGH (100-120 BPM)	0	0	0	0	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0	0
	MISSING	0	0	0	0	0	0	0
	TOTAL	36	1 (2.8%)	4 (11.1%)	29 (80.6%)	2 (5.6%)	0	0
SB 207499	LOW CONCERN (<50 BPM)	0	0	0	0	0	0	0
	LOW (50-59 BPM)	6	1 (16.7%)	3 (50.0%)	2 (33.3%)	0	0	0
	NORMAL (60-99 BPM)	49	0	1 (2.0%)	43 (87.8%)	5 (10.2%)	0	0
	HIGH (100-120 BPM)	3	0	0	1 (33.3%)	2 (66.7%)	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0	0
	MISSING	0	0	0	0	0	0	0
	TOTAL	58	1 (1.7%)	4 (6.9%)	46 (79.3%)	7 (12.1%)	0	0
TOTAL	LOW CONCERN (<50 BPM)	0	0	0	0	0	0	0
	LOW (50-59 BPM)	12	2 (16.7%)	4 (33.3%)	6 (50.0%)	0	0	0
	NORMAL (60-99 BPM)	79	0	4 (5.1%)	68 (86.1%)	7 (8.9%)	0	0
	HIGH (100-120 BPM)	3	0	0	1 (33.3%)	2 (66.7%)	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0	0
	MISSING	0	0	0	0	0	0	0
	TOTAL	94	2 (2.1%)	8 (8.5%)	75 (79.8%)	9 (9.6%)	0	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: VISIT 37/WEEK 136

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<50 BPM)	0	0	0	0	0	0
	LOW (50-59 BPM)	0	0	0	0	0	0
	NORMAL (60-99 BPM)	1	0	0	1 (100.0%)	0	0
	HIGH (100-120 BPM)	0	0	0	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	MISSING	0	0	0	0	0	0
	TOTAL	1	0	0	1 (100.0%)	0	0
SB 207499	LOW CONCERN (<50 BPM)	0	0	0	0	0	0
	LOW (50-59 BPM)	0	0	0	0	0	0
	NORMAL (60-99 BPM)	2	0	0	1 (50.0%)	1 (50.0%)	0
	HIGH (100-120 BPM)	0	0	0	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	MISSING	0	0	0	0	0	0
	TOTAL	2	0	0	1 (50.0%)	1 (50.0%)	0
TOTAL	LOW CONCERN (<50 BPM)	0	0	0	0	0	0
	LOW (50-59 BPM)	0	0	0	0	0	0
	NORMAL (60-99 BPM)	3	0	0	2 (66.7%)	1 (33.3%)	0
	HIGH (100-120 BPM)	0	0	0	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	MISSING	0	0	0	0	0	0
	TOTAL	3	0	0	2 (66.7%)	1 (33.3%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: ATRIAL RATE TIME POINT: TOTAL ON-THERAPY

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----									
			LOW CONCERN		LOW		NORMAL		HIGH		HIGH CONCERN	

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0		0	
	LOW (50-59 BPM)	25	8	(32.0%)	12	(48.0%)	2	(8.0%)	2	(8.0%)	2	(8.0%)
	NORMAL (60-99 BPM)	207	2	(1.0%)	52	(25.1%)	104	(50.2%)	48	(23.2%)	8	(3.9%)
	HIGH (100-120 BPM)	7	0		0		1	(14.3%)	6	(85.7%)	0	
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0	
	MISSING	0	0		0		0		0		0	
	TOTAL	239	10	(4.2%)	64	(26.8%)	107	(44.8%)	56	(23.4%)	10	(4.2%)
SB 207499	LOW CONCERN (<50 BPM)	7	5	(71.4%)	2	(28.6%)	0		0		1	(14.3%)
	LOW (50-59 BPM)	60	14	(23.3%)	35	(58.3%)	8	(13.3%)	2	(3.3%)	4	(6.7%)
	NORMAL (60-99 BPM)	390	8	(2.1%)	90	(23.1%)	203	(52.1%)	83	(21.3%)	15	(3.8%)
	HIGH (100-120 BPM)	12	0		2	(16.7%)	0		8	(66.7%)	3	(25.0%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0	
	MISSING	2	0		0		1	(50.0%)	1	(50.0%)	0	
	TOTAL	471	27	(5.7%)	129	(27.4%)	212	(45.0%)	94	(20.0%)	23	(4.9%)
TOTAL	LOW CONCERN (<50 BPM)	7	5	(71.4%)	2	(28.6%)	0		0		1	(14.3%)
	LOW (50-59 BPM)	85	22	(25.9%)	47	(55.3%)	10	(11.8%)	4	(4.7%)	6	(7.1%)
	NORMAL (60-99 BPM)	597	10	(1.7%)	142	(23.8%)	307	(51.4%)	131	(21.9%)	23	(3.9%)
	HIGH (100-120 BPM)	19	0		2	(10.5%)	1	(5.3%)	14	(73.7%)	3	(15.8%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0	
	MISSING	2	0		0		1	(50.0%)	1	(50.0%)	0	
	TOTAL	710	37	(5.2%)	193	(27.2%)	319	(44.9%)	150	(21.1%)	33	(4.6%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

		PARAMETER: ATRIAL RATE		TIME POINT: ENDPOINT								
PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	LOW CONCERN		LOW		-ON-THERAPY-		HIGH		HIGH CONCERN	

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0		0	
	LOW (50-59 BPM)	25	3	(12.0%)	8	(32.0%)	12	(48.0%)	1	(4.0%)	1	(4.0%)
	NORMAL (60-99 BPM)	207	0		10	(4.8%)	183	(88.4%)	13	(6.3%)	1	(0.5%)
	HIGH (100-120 BPM)	7	0		0		5	(71.4%)	2	(28.6%)	0	
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0	
	MISSING	0	0		0		0		0		0	
	TOTAL	239	3	(1.3%)	18	(7.5%)	200	(83.7%)	16	(6.7%)	2	(0.8%)
SB 207499	LOW CONCERN (<50 BPM)	7	2	(28.6%)	2	(28.6%)	3	(42.9%)	0		0	
	LOW (50-59 BPM)	60	2	(3.3%)	20	(33.3%)	37	(61.7%)	1	(1.7%)	0	
	NORMAL (60-99 BPM)	390	0		19	(4.9%)	348	(89.2%)	22	(5.6%)	1	(0.3%)
	HIGH (100-120 BPM)	12	0		0		7	(58.3%)	4	(33.3%)	1	(8.3%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0	
	MISSING	2	0		0		2	(100.0%)	0		0	
	TOTAL	471	4	(0.8%)	41	(8.7%)	397	(84.3%)	27	(5.7%)	2	(0.4%)
TOTAL	LOW CONCERN (<50 BPM)	7	2	(28.6%)	2	(28.6%)	3	(42.9%)	0		0	
	LOW (50-59 BPM)	85	5	(5.9%)	28	(32.9%)	49	(57.6%)	2	(2.4%)	1	(1.2%)
	NORMAL (60-99 BPM)	597	0		29	(4.9%)	531	(88.9%)	35	(5.9%)	2	(0.3%)
	HIGH (100-120 BPM)	19	0		0		12	(63.2%)	6	(31.6%)	1	(5.3%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0	
	MISSING	2	0		0		2	(100.0%)	0		0	
	TOTAL	710	7	(1.0%)	59	(8.3%)	597	(84.1%)	43	(6.1%)	4	(0.6%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 2/WEEK 1

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----									
			LOW CONCERN		LOW		NORMAL		HIGH		HIGH CONCERN	

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0		0	
	LOW (50-59 BPM)	24	3	(12.5%)	9	(37.5%)	12	(50.0%)	0		0	
	NORMAL (60-99 BPM)	203	0		6	(3.0%)	188	(92.6%)	8	(3.9%)	1	(0.5%)
	HIGH (100-120 BPM)	7	0		0		6	(85.7%)	1	(14.3%)	0	
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0	
	TOTAL	234	3	(1.3%)	15	(6.4%)	206	(88.0%)	9	(3.8%)	1	(0.4%)
SB 207499	LOW CONCERN (<50 BPM)	6	2	(33.3%)	1	(16.7%)	3	(50.0%)	0		0	
	LOW (50-59 BPM)	60	2	(3.3%)	19	(31.7%)	38	(63.3%)	1	(1.7%)	0	
	NORMAL (60-99 BPM)	384	3	(0.8%)	20	(5.2%)	349	(90.9%)	11	(2.9%)	1	(0.3%)
	HIGH (100-120 BPM)	12	0		0		7	(58.3%)	5	(41.7%)	0	
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0	
	TOTAL	462	7	(1.5%)	40	(8.7%)	397	(85.9%)	17	(3.7%)	1	(0.2%)
TOTAL	LOW CONCERN (<50 BPM)	6	2	(33.3%)	1	(16.7%)	3	(50.0%)	0		0	
	LOW (50-59 BPM)	84	5	(6.0%)	28	(33.3%)	50	(59.5%)	1	(1.2%)	0	
	NORMAL (60-99 BPM)	587	3	(0.5%)	26	(4.4%)	537	(91.5%)	19	(3.2%)	2	(0.3%)
	HIGH (100-120 BPM)	19	0		0		13	(68.4%)	6	(31.6%)	0	
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0	
	TOTAL	696	10	(1.4%)	55	(7.9%)	603	(86.6%)	26	(3.7%)	2	(0.3%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 3/WEEK 2

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----								
			LOW CONCERN		LOW		NORMAL		HIGH		HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0		0
	LOW (50-59 BPM)	24	0		12	(50.0%)	12	(50.0%)	0		0
	NORMAL (60-99 BPM)	192	0		16	(8.3%)	170	(88.5%)	6	(3.1%)	0
	HIGH (100-120 BPM)	7	0		0		6	(85.7%)	1	(14.3%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	223	0		28	(12.6%)	188	(84.3%)	7	(3.1%)	0
SB 207499	LOW CONCERN (<50 BPM)	6	1	(16.7%)	2	(33.3%)	2	(33.3%)	1	(16.7%)	0
	LOW (50-59 BPM)	58	2	(3.4%)	19	(32.8%)	36	(62.1%)	0		1 (1.7%)
	NORMAL (60-99 BPM)	376	0		27	(7.2%)	341	(90.7%)	8	(2.1%)	0
	HIGH (100-120 BPM)	12	0		0		8	(66.7%)	4	(33.3%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	452	3	(0.7%)	48	(10.6%)	387	(85.6%)	13	(2.9%)	1 (0.2%)
TOTAL	LOW CONCERN (<50 BPM)	6	1	(16.7%)	2	(33.3%)	2	(33.3%)	1	(16.7%)	0
	LOW (50-59 BPM)	82	2	(2.4%)	31	(37.8%)	48	(58.5%)	0		1 (1.2%)
	NORMAL (60-99 BPM)	568	0		43	(7.6%)	511	(90.0%)	14	(2.5%)	0
	HIGH (100-120 BPM)	19	0		0		14	(73.7%)	5	(26.3%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	675	3	(0.4%)	76	(11.3%)	575	(85.2%)	20	(3.0%)	1 (0.1%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 4/WEEK 4

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----								
			LOW CONCERN		LOW		NORMAL		HIGH		HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0		0
	LOW (50-59 BPM)	23	1 (4.3%)		10 (43.5%)		12 (52.2%)		0		0
	NORMAL (60-99 BPM)	185	0		14 (7.6%)		161 (87.0%)		9 (4.9%)		1 (0.5%)
	HIGH (100-120 BPM)	7	0		0		6 (85.7%)		1 (14.3%)		0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	215	1 (0.5%)		24 (11.2%)		179 (83.3%)		10 (4.7%)		1 (0.5%)
SB 207499	LOW CONCERN (<50 BPM)	6	1 (16.7%)		3 (50.0%)		2 (33.3%)		0		0
	LOW (50-59 BPM)	59	3 (5.1%)		22 (37.3%)		33 (55.9%)		1 (1.7%)		0
	NORMAL (60-99 BPM)	381	0		23 (6.0%)		344 (90.3%)		13 (3.4%)		1 (0.3%)
	HIGH (100-120 BPM)	12	0		0		8 (66.7%)		4 (33.3%)		0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	458	4 (0.9%)		48 (10.5%)		387 (84.5%)		18 (3.9%)		1 (0.2%)
TOTAL	LOW CONCERN (<50 BPM)	6	1 (16.7%)		3 (50.0%)		2 (33.3%)		0		0
	LOW (50-59 BPM)	82	4 (4.9%)		32 (39.0%)		45 (54.9%)		1 (1.2%)		0
	NORMAL (60-99 BPM)	566	0		37 (6.5%)		505 (89.2%)		22 (3.9%)		2 (0.4%)
	HIGH (100-120 BPM)	19	0		0		14 (73.7%)		5 (26.3%)		0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	673	5 (0.7%)		72 (10.7%)		566 (84.1%)		28 (4.2%)		2 (0.3%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 5/WEEK 8

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN			
PLACEBO	LOW CONCERN (<50 BPM)	0	0	0	0	0	0	0		
	LOW (50-59 BPM)	23	0	11 (47.8%)	11 (47.8%)	1 (4.3%)	0			
	NORMAL (60-99 BPM)	183	0	12 (6.6%)	162 (88.5%)	8 (4.4%)	1 (0.5%)			
	HIGH (100-120 BPM)	7	0	0	6 (85.7%)	1 (14.3%)	0			
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0			
	TOTAL	213	0	23 (10.8%)	179 (84.0%)	10 (4.7%)	1 (0.5%)			
SB 207499	LOW CONCERN (<50 BPM)	6	2 (33.3%)	2 (33.3%)	2 (33.3%)	0	0			
	LOW (50-59 BPM)	59	6 (10.2%)	24 (40.7%)	27 (45.8%)	2 (3.4%)	0			
	NORMAL (60-99 BPM)	370	0	19 (5.1%)	342 (92.4%)	7 (1.9%)	2 (0.5%)			
	HIGH (100-120 BPM)	12	0	0	7 (58.3%)	5 (41.7%)	0			
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0			
	TOTAL	447	8 (1.8%)	45 (10.1%)	378 (84.6%)	14 (3.1%)	2 (0.4%)			
TOTAL	LOW CONCERN (<50 BPM)	6	2 (33.3%)	2 (33.3%)	2 (33.3%)	0	0			
	LOW (50-59 BPM)	82	6 (7.3%)	35 (42.7%)	38 (46.3%)	3 (3.7%)	0			
	NORMAL (60-99 BPM)	553	0	31 (5.6%)	504 (91.1%)	15 (2.7%)	3 (0.5%)			
	HIGH (100-120 BPM)	19	0	0	13 (68.4%)	6 (31.6%)	0			
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0			
	TOTAL	660	8 (1.2%)	68 (10.3%)	557 (84.4%)	24 (3.6%)	3 (0.5%)			

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 6/WEEK 12

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN		LOW		NORMAL		HIGH	HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	
	LOW (50-59 BPM)	23	1 (4.3%)		12 (52.2%)		8 (34.8%)		2 (8.7%)	0
	NORMAL (60-99 BPM)	179	0		12 (6.7%)		156 (87.2%)		11 (6.1%)	0
	HIGH (100-120 BPM)	6	0		0		4 (66.7%)		2 (33.3%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	TOTAL	208	1 (0.5%)		24 (11.5%)		168 (80.8%)		15 (7.2%)	0
SB 207499	LOW CONCERN (<50 BPM)	6	2 (33.3%)		2 (33.3%)		2 (33.3%)		0	0
	LOW (50-59 BPM)	56	5 (8.9%)		20 (35.7%)		29 (51.8%)		2 (3.6%)	0
	NORMAL (60-99 BPM)	370	1 (0.3%)		18 (4.9%)		341 (92.2%)		10 (2.7%)	0
	HIGH (100-120 BPM)	12	0		0		9 (75.0%)		3 (25.0%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	TOTAL	444	8 (1.8%)		40 (9.0%)		381 (85.8%)		15 (3.4%)	0
TOTAL	LOW CONCERN (<50 BPM)	6	2 (33.3%)		2 (33.3%)		2 (33.3%)		0	0
	LOW (50-59 BPM)	79	6 (7.6%)		32 (40.5%)		37 (46.8%)		4 (5.1%)	0
	NORMAL (60-99 BPM)	549	1 (0.2%)		30 (5.5%)		497 (90.5%)		21 (3.8%)	0
	HIGH (100-120 BPM)	18	0		0		13 (72.2%)		5 (27.8%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	TOTAL	652	9 (1.4%)		64 (9.8%)		549 (84.2%)		30 (4.6%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 7/WEEK 16

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----									
			LOW CONCERN		LOW		NORMAL		HIGH		HIGH CONCERN	

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0		0	
	LOW (50-59 BPM)	23	1	(4.3%)	10	(43.5%)	11	(47.8%)	1	(4.3%)	0	
	NORMAL (60-99 BPM)	173	1	(0.6%)	10	(5.8%)	154	(89.0%)	8	(4.6%)	0	
	HIGH (100-120 BPM)	6	0		0		4	(66.7%)	2	(33.3%)	0	
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0	
	TOTAL	202	2	(1.0%)	20	(9.9%)	169	(83.7%)	11	(5.4%)	0	
SB 207499	LOW CONCERN (<50 BPM)	6	1	(16.7%)	4	(66.7%)	0		1	(16.7%)	0	
	LOW (50-59 BPM)	54	4	(7.4%)	22	(40.7%)	28	(51.9%)	0		0	
	NORMAL (60-99 BPM)	364	0		19	(5.2%)	331	(90.9%)	13	(3.6%)	1	(0.3%)
	HIGH (100-120 BPM)	12	0		0		7	(58.3%)	5	(41.7%)	0	
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0	
	TOTAL	436	5	(1.1%)	45	(10.3%)	366	(83.9%)	19	(4.4%)	1	(0.2%)
TOTAL	LOW CONCERN (<50 BPM)	6	1	(16.7%)	4	(66.7%)	0		1	(16.7%)	0	
	LOW (50-59 BPM)	77	5	(6.5%)	32	(41.6%)	39	(50.6%)	1	(1.3%)	0	
	NORMAL (60-99 BPM)	537	1	(0.2%)	29	(5.4%)	485	(90.3%)	21	(3.9%)	1	(0.2%)
	HIGH (100-120 BPM)	18	0		0		11	(61.1%)	7	(38.9%)	0	
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0	
	TOTAL	638	7	(1.1%)	65	(10.2%)	535	(83.9%)	30	(4.7%)	1	(0.2%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 8/WEEK 20

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN		LOW		NORMAL		HIGH	

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	
	LOW (50-59 BPM)	23	3	(13.0%)	8	(34.8%)	10	(43.5%)	2	(8.7%)
	NORMAL (60-99 BPM)	169	0		13	(7.7%)	148	(87.6%)	8	(4.7%)
	HIGH (100-120 BPM)	5	0		0		5	(100.0%)	0	
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	
	TOTAL	197	3	(1.5%)	21	(10.7%)	163	(82.7%)	10	(5.1%)
SB 207499	LOW CONCERN (<50 BPM)	6	3	(50.0%)	2	(33.3%)	1	(16.7%)	0	
	LOW (50-59 BPM)	54	7	(13.0%)	19	(35.2%)	28	(51.9%)	0	
	NORMAL (60-99 BPM)	360	0		12	(3.3%)	334	(92.8%)	14	(3.9%)
	HIGH (100-120 BPM)	12	0		1	(8.3%)	8	(66.7%)	3	(25.0%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	
	TOTAL	432	10	(2.3%)	34	(7.9%)	371	(85.9%)	17	(3.9%)
TOTAL	LOW CONCERN (<50 BPM)	6	3	(50.0%)	2	(33.3%)	1	(16.7%)	0	
	LOW (50-59 BPM)	77	10	(13.0%)	27	(35.1%)	38	(49.4%)	2	(2.6%)
	NORMAL (60-99 BPM)	529	0		25	(4.7%)	482	(91.1%)	22	(4.2%)
	HIGH (100-120 BPM)	17	0		1	(5.9%)	13	(76.5%)	3	(17.6%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	
	TOTAL	629	13	(2.1%)	55	(8.7%)	534	(84.9%)	27	(4.3%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 9/WEEK 24

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----								
			LOW CONCERN		LOW		NORMAL		HIGH		HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0		0
	LOW (50-59 BPM)	22	1	(4.5%)	9	(40.9%)	10	(45.5%)	2	(9.1%)	0
	NORMAL (60-99 BPM)	166	0		8	(4.8%)	148	(89.2%)	9	(5.4%)	1 (0.6%)
	HIGH (100-120 BPM)	5	0		0		5	(100.0%)	0		0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	193	1	(0.5%)	17	(8.8%)	163	(84.5%)	11	(5.7%)	1 (0.5%)
SB 207499	LOW CONCERN (<50 BPM)	6	1	(16.7%)	3	(50.0%)	2	(33.3%)	0		0
	LOW (50-59 BPM)	53	6	(11.3%)	19	(35.8%)	28	(52.8%)	0		0
	NORMAL (60-99 BPM)	356	0		19	(5.3%)	320	(89.9%)	16	(4.5%)	1 (0.3%)
	HIGH (100-120 BPM)	12	0		0		9	(75.0%)	2	(16.7%)	1 (8.3%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	427	7	(1.6%)	41	(9.6%)	359	(84.1%)	18	(4.2%)	2 (0.5%)
TOTAL	LOW CONCERN (<50 BPM)	6	1	(16.7%)	3	(50.0%)	2	(33.3%)	0		0
	LOW (50-59 BPM)	75	7	(9.3%)	28	(37.3%)	38	(50.7%)	2	(2.7%)	0
	NORMAL (60-99 BPM)	522	0		27	(5.2%)	468	(89.7%)	25	(4.8%)	2 (0.4%)
	HIGH (100-120 BPM)	17	0		0		14	(82.4%)	2	(11.8%)	1 (5.9%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	620	8	(1.3%)	58	(9.4%)	522	(84.2%)	29	(4.7%)	3 (0.5%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 10/WEEK 28

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----								
			LOW CONCERN		LOW		NORMAL		HIGH	HIGH CONCERN	

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0		
	LOW (50-59 BPM)	21	1	(4.8%)	7	(33.3%)	13	(61.9%)	0	0	
	NORMAL (60-99 BPM)	164	1	(0.6%)	11	(6.7%)	142	(86.6%)	9	(5.5%)	1 (0.6%)
	HIGH (100-120 BPM)	5	0		0		5	(100.0%)	0	0	
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0	
	TOTAL	190	2	(1.1%)	18	(9.5%)	160	(84.2%)	9	(4.7%)	1 (0.5%)
SB 207499	LOW CONCERN (<50 BPM)	6	3	(50.0%)	2	(33.3%)	1	(16.7%)	0	0	
	LOW (50-59 BPM)	52	3	(5.8%)	20	(38.5%)	29	(55.8%)	0	0	
	NORMAL (60-99 BPM)	352	1	(0.3%)	16	(4.5%)	324	(92.0%)	11	(3.1%)	0
	HIGH (100-120 BPM)	12	0		0		9	(75.0%)	2	(16.7%)	1 (8.3%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0	
	TOTAL	422	7	(1.7%)	38	(9.0%)	363	(86.0%)	13	(3.1%)	1 (0.2%)
TOTAL	LOW CONCERN (<50 BPM)	6	3	(50.0%)	2	(33.3%)	1	(16.7%)	0	0	
	LOW (50-59 BPM)	73	4	(5.5%)	27	(37.0%)	42	(57.5%)	0	0	
	NORMAL (60-99 BPM)	516	2	(0.4%)	27	(5.2%)	466	(90.3%)	20	(3.9%)	1 (0.2%)
	HIGH (100-120 BPM)	17	0		0		14	(82.4%)	2	(11.8%)	1 (5.9%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0	
	TOTAL	612	9	(1.5%)	56	(9.2%)	523	(85.5%)	22	(3.6%)	2 (0.3%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 11/WEEK 32

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----								
			LOW CONCERN		LOW		NORMAL		HIGH		HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0		0
	LOW (50-59 BPM)	21	1	(4.8%)	9	(42.9%)	10	(47.6%)	1	(4.8%)	0
	NORMAL (60-99 BPM)	160	1	(0.6%)	11	(6.9%)	145	(90.6%)	3	(1.9%)	0
	HIGH (100-120 BPM)	5	0		0		2	(40.0%)	3	(60.0%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	186	2	(1.1%)	20	(10.8%)	157	(84.4%)	7	(3.8%)	0
SB 207499	LOW CONCERN (<50 BPM)	6	1	(16.7%)	4	(66.7%)	1	(16.7%)	0		0
	LOW (50-59 BPM)	52	5	(9.6%)	18	(34.6%)	28	(53.8%)	1	(1.9%)	0
	NORMAL (60-99 BPM)	349	0		15	(4.3%)	321	(92.0%)	12	(3.4%)	1 (0.3%)
	HIGH (100-120 BPM)	12	0		0		5	(41.7%)	7	(58.3%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	419	6	(1.4%)	37	(8.8%)	355	(84.7%)	20	(4.8%)	1 (0.2%)
TOTAL	LOW CONCERN (<50 BPM)	6	1	(16.7%)	4	(66.7%)	1	(16.7%)	0		0
	LOW (50-59 BPM)	73	6	(8.2%)	27	(37.0%)	38	(52.1%)	2	(2.7%)	0
	NORMAL (60-99 BPM)	509	1	(0.2%)	26	(5.1%)	466	(91.6%)	15	(2.9%)	1 (0.2%)
	HIGH (100-120 BPM)	17	0		0		7	(41.2%)	10	(58.8%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	605	8	(1.3%)	57	(9.4%)	512	(84.6%)	27	(4.5%)	1 (0.2%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 12/WEEK 36

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN		LOW		NORMAL		HIGH	HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	
	LOW (50-59 BPM)	21	0		9	(42.9%)	10	(47.6%)	2	(9.5%)
	NORMAL (60-99 BPM)	161	0		12	(7.5%)	141	(87.6%)	7	(4.3%)
	HIGH (100-120 BPM)	5	0		0		2	(40.0%)	3	(60.0%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	
	TOTAL	187	0		21	(11.2%)	153	(81.8%)	12	(6.4%)
SB 207499	LOW CONCERN (<50 BPM)	6	2	(33.3%)	4	(66.7%)	0		0	
	LOW (50-59 BPM)	52	4	(7.7%)	18	(34.6%)	30	(57.7%)	0	
	NORMAL (60-99 BPM)	341	0		15	(4.4%)	314	(92.1%)	11	(3.2%)
	HIGH (100-120 BPM)	11	0		0		8	(72.7%)	3	(27.3%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	
	TOTAL	410	6	(1.5%)	37	(9.0%)	352	(85.9%)	14	(3.4%)
TOTAL	LOW CONCERN (<50 BPM)	6	2	(33.3%)	4	(66.7%)	0		0	
	LOW (50-59 BPM)	73	4	(5.5%)	27	(37.0%)	40	(54.8%)	2	(2.7%)
	NORMAL (60-99 BPM)	502	0		27	(5.4%)	455	(90.6%)	18	(3.6%)
	HIGH (100-120 BPM)	16	0		0		10	(62.5%)	6	(37.5%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	
	TOTAL	597	6	(1.0%)	58	(9.7%)	505	(84.6%)	26	(4.4%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 13/WEEK 40

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN		LOW		NORMAL		HIGH	HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	
	LOW (50-59 BPM)	21	1 (4.8%)		10 (47.6%)		9 (42.9%)		1 (4.8%)	0
	NORMAL (60-99 BPM)	159	0		10 (6.3%)		144 (90.6%)		5 (3.1%)	0
	HIGH (100-120 BPM)	5	0		0		3 (60.0%)		2 (40.0%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	TOTAL	185	1 (0.5%)		20 (10.8%)		156 (84.3%)		8 (4.3%)	0
SB 207499	LOW CONCERN (<50 BPM)	6	1 (16.7%)		4 (66.7%)		1 (16.7%)		0	0
	LOW (50-59 BPM)	52	4 (7.7%)		22 (42.3%)		26 (50.0%)		0	0
	NORMAL (60-99 BPM)	336	0		12 (3.6%)		311 (92.6%)		13 (3.9%)	0
	HIGH (100-120 BPM)	11	0		0		9 (81.8%)		2 (18.2%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	TOTAL	405	5 (1.2%)		38 (9.4%)		347 (85.7%)		15 (3.7%)	0
TOTAL	LOW CONCERN (<50 BPM)	6	1 (16.7%)		4 (66.7%)		1 (16.7%)		0	0
	LOW (50-59 BPM)	73	5 (6.8%)		32 (43.8%)		35 (47.9%)		1 (1.4%)	0
	NORMAL (60-99 BPM)	495	0		22 (4.4%)		455 (91.9%)		18 (3.6%)	0
	HIGH (100-120 BPM)	16	0		0		12 (75.0%)		4 (25.0%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	TOTAL	590	6 (1.0%)		58 (9.8%)		503 (85.3%)		23 (3.9%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 14/WEEK 44

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----									
			LOW CONCERN		LOW		NORMAL		HIGH		HIGH CONCERN	

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0		0	
	LOW (50-59 BPM)	20	3	(15.0%)	4	(20.0%)	12	(60.0%)	0		1	(5.0%)
	NORMAL (60-99 BPM)	158	0		16	(10.1%)	133	(84.2%)	9	(5.7%)	0	
	HIGH (100-120 BPM)	5	0		0		4	(80.0%)	1	(20.0%)	0	
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0	
	TOTAL	183	3	(1.6%)	20	(10.9%)	149	(81.4%)	10	(5.5%)	1	(0.5%)
SB 207499	LOW CONCERN (<50 BPM)	6	2	(33.3%)	4	(66.7%)	0		0		0	
	LOW (50-59 BPM)	52	3	(5.8%)	16	(30.8%)	32	(61.5%)	0		1	(1.9%)
	NORMAL (60-99 BPM)	335	2	(0.6%)	14	(4.2%)	306	(91.3%)	12	(3.6%)	1	(0.3%)
	HIGH (100-120 BPM)	11	0		1	(9.1%)	8	(72.7%)	2	(18.2%)	0	
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0	
	TOTAL	404	7	(1.7%)	35	(8.7%)	346	(85.6%)	14	(3.5%)	2	(0.5%)
TOTAL	LOW CONCERN (<50 BPM)	6	2	(33.3%)	4	(66.7%)	0		0		0	
	LOW (50-59 BPM)	72	6	(8.3%)	20	(27.8%)	44	(61.1%)	0		2	(2.8%)
	NORMAL (60-99 BPM)	493	2	(0.4%)	30	(6.1%)	439	(89.0%)	21	(4.3%)	1	(0.2%)
	HIGH (100-120 BPM)	16	0		1	(6.3%)	12	(75.0%)	3	(18.8%)	0	
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0	
	TOTAL	587	10	(1.7%)	55	(9.4%)	495	(84.3%)	24	(4.1%)	3	(0.5%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 15/WEEK 48

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----								
			LOW CONCERN		LOW		NORMAL		HIGH		HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0		0
	LOW (50-59 BPM)	20	1	(5.0%)	8	(40.0%)	11	(55.0%)	0		0
	NORMAL (60-99 BPM)	159	0		12	(7.5%)	133	(83.6%)	13	(8.2%)	1 (0.6%)
	HIGH (100-120 BPM)	5	0		0		4	(80.0%)	1	(20.0%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	184	1	(0.5%)	20	(10.9%)	148	(80.4%)	14	(7.6%)	1 (0.5%)
SB 207499	LOW CONCERN (<50 BPM)	6	2	(33.3%)	3	(50.0%)	1	(16.7%)	0		0
	LOW (50-59 BPM)	52	2	(3.8%)	21	(40.4%)	29	(55.8%)	0		0
	NORMAL (60-99 BPM)	329	0		23	(7.0%)	291	(88.4%)	14	(4.3%)	1 (0.3%)
	HIGH (100-120 BPM)	11	0		0		9	(81.8%)	2	(18.2%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	398	4	(1.0%)	47	(11.8%)	330	(82.9%)	16	(4.0%)	1 (0.3%)
TOTAL	LOW CONCERN (<50 BPM)	6	2	(33.3%)	3	(50.0%)	1	(16.7%)	0		0
	LOW (50-59 BPM)	72	3	(4.2%)	29	(40.3%)	40	(55.6%)	0		0
	NORMAL (60-99 BPM)	488	0		35	(7.2%)	424	(86.9%)	27	(5.5%)	2 (0.4%)
	HIGH (100-120 BPM)	16	0		0		13	(81.3%)	3	(18.8%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	582	5	(0.9%)	67	(11.5%)	478	(82.1%)	30	(5.2%)	2 (0.3%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 16/WEEK 52

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN		LOW		NORMAL		HIGH	HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	
	LOW (50-59 BPM)	20	2	(10.0%)	7	(35.0%)	11	(55.0%)	0	0
	NORMAL (60-99 BPM)	156	0		10	(6.4%)	140	(89.7%)	6	(3.8%)
	HIGH (100-120 BPM)	4	0		0		3	(75.0%)	1	(25.0%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	TOTAL	180	2	(1.1%)	17	(9.4%)	154	(85.6%)	7	(3.9%)
SB 207499	LOW CONCERN (<50 BPM)	6	0		4	(66.7%)	2	(33.3%)	0	0
	LOW (50-59 BPM)	48	3	(6.3%)	17	(35.4%)	28	(58.3%)	0	0
	NORMAL (60-99 BPM)	320	0		16	(5.0%)	293	(91.6%)	11	(3.4%)
	HIGH (100-120 BPM)	10	0		0		8	(80.0%)	2	(20.0%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	TOTAL	384	3	(0.8%)	37	(9.6%)	331	(86.2%)	13	(3.4%)
TOTAL	LOW CONCERN (<50 BPM)	6	0		4	(66.7%)	2	(33.3%)	0	0
	LOW (50-59 BPM)	68	5	(7.4%)	24	(35.3%)	39	(57.4%)	0	0
	NORMAL (60-99 BPM)	476	0		26	(5.5%)	433	(91.0%)	17	(3.6%)
	HIGH (100-120 BPM)	14	0		0		11	(78.6%)	3	(21.4%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	TOTAL	564	5	(0.9%)	54	(9.6%)	485	(86.0%)	20	(3.5%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 17/WEEK 56

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----								
			LOW CONCERN		LOW		NORMAL		HIGH		HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0		0
	LOW (50-59 BPM)	19	3 (15.8%)		6 (31.6%)		10 (52.6%)		0		0
	NORMAL (60-99 BPM)	147	0		9 (6.1%)		128 (87.1%)		10 (6.8%)		0
	HIGH (100-120 BPM)	3	0		0		2 (66.7%)		1 (33.3%)		0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	169	3 (1.8%)		15 (8.9%)		140 (82.8%)		11 (6.5%)		0
SB 207499	LOW CONCERN (<50 BPM)	6	2 (33.3%)		2 (33.3%)		2 (33.3%)		0		0
	LOW (50-59 BPM)	46	2 (4.3%)		15 (32.6%)		28 (60.9%)		0		1 (2.2%)
	NORMAL (60-99 BPM)	302	0		16 (5.3%)		270 (89.4%)		14 (4.6%)		2 (0.7%)
	HIGH (100-120 BPM)	10	0		0		7 (70.0%)		3 (30.0%)		0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	364	4 (1.1%)		33 (9.1%)		307 (84.3%)		17 (4.7%)		3 (0.8%)
TOTAL	LOW CONCERN (<50 BPM)	6	2 (33.3%)		2 (33.3%)		2 (33.3%)		0		0
	LOW (50-59 BPM)	65	5 (7.7%)		21 (32.3%)		38 (58.5%)		0		1 (1.5%)
	NORMAL (60-99 BPM)	449	0		25 (5.6%)		398 (88.6%)		24 (5.3%)		2 (0.4%)
	HIGH (100-120 BPM)	13	0		0		9 (69.2%)		4 (30.8%)		0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	533	7 (1.3%)		48 (9.0%)		447 (83.9%)		28 (5.3%)		3 (0.6%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 18/WEEK 60

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----								
			LOW CONCERN		LOW		NORMAL		HIGH		HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0		0
	LOW (50-59 BPM)	19	1	(5.3%)	6	(31.6%)	12	(63.2%)	0		0
	NORMAL (60-99 BPM)	150	0		15	(10.0%)	124	(82.7%)	9	(6.0%)	2 (1.3%)
	HIGH (100-120 BPM)	4	0		0		2	(50.0%)	2	(50.0%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	173	1	(0.6%)	21	(12.1%)	138	(79.8%)	11	(6.4%)	2 (1.2%)
SB 207499	LOW CONCERN (<50 BPM)	6	1	(16.7%)	2	(33.3%)	3	(50.0%)	0		0
	LOW (50-59 BPM)	48	3	(6.3%)	10	(20.8%)	34	(70.8%)	1	(2.1%)	0
	NORMAL (60-99 BPM)	310	0		15	(4.8%)	278	(89.7%)	17	(5.5%)	0
	HIGH (100-120 BPM)	10	0		0		8	(80.0%)	1	(10.0%)	1 (10.0%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	374	4	(1.1%)	27	(7.2%)	323	(86.4%)	19	(5.1%)	1 (0.3%)
TOTAL	LOW CONCERN (<50 BPM)	6	1	(16.7%)	2	(33.3%)	3	(50.0%)	0		0
	LOW (50-59 BPM)	67	4	(6.0%)	16	(23.9%)	46	(68.7%)	1	(1.5%)	0
	NORMAL (60-99 BPM)	460	0		30	(6.5%)	402	(87.4%)	26	(5.7%)	2 (0.4%)
	HIGH (100-120 BPM)	14	0		0		10	(71.4%)	3	(21.4%)	1 (7.1%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	547	5	(0.9%)	48	(8.8%)	461	(84.3%)	30	(5.5%)	3 (0.5%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 19/WEEK 64

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN		LOW		NORMAL		HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	0
	LOW (50-59 BPM)	15	2	(13.3%)	5	(33.3%)	8	(53.3%)	0	0
	NORMAL (60-99 BPM)	125	0		9	(7.2%)	110	(88.0%)	6	(4.8%) 0
	HIGH (100-120 BPM)	2	0		0		2	(100.0%)	0	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	TOTAL	142	2	(1.4%)	14	(9.9%)	120	(84.5%)	6	(4.2%) 0
SB 207499	LOW CONCERN (<50 BPM)	4	3	(75.0%)	1	(25.0%)	0		0	0
	LOW (50-59 BPM)	33	1	(3.0%)	8	(24.2%)	23	(69.7%)	1	(3.0%) 0
	NORMAL (60-99 BPM)	262	1	(0.4%)	9	(3.4%)	239	(91.2%)	13	(5.0%) 0
	HIGH (100-120 BPM)	9	0		0		5	(55.6%)	4	(44.4%) 0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	TOTAL	308	5	(1.6%)	18	(5.8%)	267	(86.7%)	18	(5.8%) 0
TOTAL	LOW CONCERN (<50 BPM)	4	3	(75.0%)	1	(25.0%)	0		0	0
	LOW (50-59 BPM)	48	3	(6.3%)	13	(27.1%)	31	(64.6%)	1	(2.1%) 0
	NORMAL (60-99 BPM)	387	1	(0.3%)	18	(4.7%)	349	(90.2%)	19	(4.9%) 0
	HIGH (100-120 BPM)	11	0		0		7	(63.6%)	4	(36.4%) 0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	TOTAL	450	7	(1.6%)	32	(7.1%)	387	(86.0%)	24	(5.3%) 0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 20/WEEK 68

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----								
			LOW CONCERN		LOW		NORMAL		HIGH		HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0		0
	LOW (50-59 BPM)	15	2	(13.3%)	6	(40.0%)	7	(46.7%)	0		0
	NORMAL (60-99 BPM)	123	0		5	(4.1%)	112	(91.1%)	6	(4.9%)	0
	HIGH (100-120 BPM)	2	0		0		1	(50.0%)	1	(50.0%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	140	2	(1.4%)	11	(7.9%)	120	(85.7%)	7	(5.0%)	0
SB 207499	LOW CONCERN (<50 BPM)	4	1	(25.0%)	2	(50.0%)	1	(25.0%)	0		0
	LOW (50-59 BPM)	30	1	(3.3%)	9	(30.0%)	20	(66.7%)	0		0
	NORMAL (60-99 BPM)	252	0		13	(5.2%)	227	(90.1%)	11	(4.4%)	1 (0.4%)
	HIGH (100-120 BPM)	9	0		0		7	(77.8%)	2	(22.2%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	295	2	(0.7%)	24	(8.1%)	255	(86.4%)	13	(4.4%)	1 (0.3%)
TOTAL	LOW CONCERN (<50 BPM)	4	1	(25.0%)	2	(50.0%)	1	(25.0%)	0		0
	LOW (50-59 BPM)	45	3	(6.7%)	15	(33.3%)	27	(60.0%)	0		0
	NORMAL (60-99 BPM)	375	0		18	(4.8%)	339	(90.4%)	17	(4.5%)	1 (0.3%)
	HIGH (100-120 BPM)	11	0		0		8	(72.7%)	3	(27.3%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	435	4	(0.9%)	35	(8.0%)	375	(86.2%)	20	(4.6%)	1 (0.2%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 21/WEEK 72

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----								
			LOW CONCERN		LOW		NORMAL		HIGH		HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0		0
	LOW (50-59 BPM)	19	2	(10.5%)	6	(31.6%)	10	(52.6%)	1	(5.3%)	0
	NORMAL (60-99 BPM)	147	0		11	(7.5%)	129	(87.8%)	7	(4.8%)	0
	HIGH (100-120 BPM)	4	0		0		4	(100.0%)	0		0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	170	2	(1.2%)	17	(10.0%)	143	(84.1%)	8	(4.7%)	0
SB 207499	LOW CONCERN (<50 BPM)	6	3	(50.0%)	2	(33.3%)	1	(16.7%)	0		0
	LOW (50-59 BPM)	47	3	(6.4%)	20	(42.6%)	23	(48.9%)	1	(2.1%)	0
	NORMAL (60-99 BPM)	294	2	(0.7%)	16	(5.4%)	264	(89.8%)	12	(4.1%)	0
	HIGH (100-120 BPM)	10	0		0		5	(50.0%)	4	(40.0%)	1 (10.0%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	357	8	(2.2%)	38	(10.6%)	293	(82.1%)	17	(4.8%)	1 (0.3%)
TOTAL	LOW CONCERN (<50 BPM)	6	3	(50.0%)	2	(33.3%)	1	(16.7%)	0		0
	LOW (50-59 BPM)	66	5	(7.6%)	26	(39.4%)	33	(50.0%)	2	(3.0%)	0
	NORMAL (60-99 BPM)	441	2	(0.5%)	27	(6.1%)	393	(89.1%)	19	(4.3%)	0
	HIGH (100-120 BPM)	14	0		0		9	(64.3%)	4	(28.6%)	1 (7.1%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	527	10	(1.9%)	55	(10.4%)	436	(82.7%)	25	(4.7%)	1 (0.2%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 22/WEEK 76

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN	
PLACEBO	LOW CONCERN (<50 BPM)	0	0	0	0	0	0	
	LOW (50-59 BPM)	12	0	4 (33.3%)	8 (66.7%)	0	0	
	NORMAL (60-99 BPM)	86	0	5 (5.8%)	73 (84.9%)	6 (7.0%)	2 (2.3%)	
	HIGH (100-120 BPM)	2	0	0	1 (50.0%)	1 (50.0%)	0	
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0	
	TOTAL	100	0	9 (9.0%)	82 (82.0%)	7 (7.0%)	2 (2.0%)	
SB 207499	LOW CONCERN (<50 BPM)	3	0	2 (66.7%)	0	1 (33.3%)	0	
	LOW (50-59 BPM)	19	0	9 (47.4%)	10 (52.6%)	0	0	
	NORMAL (60-99 BPM)	170	0	6 (3.5%)	158 (92.9%)	6 (3.5%)	0	
	HIGH (100-120 BPM)	6	0	0	4 (66.7%)	2 (33.3%)	0	
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0	
	TOTAL	198	0	17 (8.6%)	172 (86.9%)	9 (4.5%)	0	
TOTAL	LOW CONCERN (<50 BPM)	3	0	2 (66.7%)	0	1 (33.3%)	0	
	LOW (50-59 BPM)	31	0	13 (41.9%)	18 (58.1%)	0	0	
	NORMAL (60-99 BPM)	256	0	11 (4.3%)	231 (90.2%)	12 (4.7%)	2 (0.8%)	
	HIGH (100-120 BPM)	8	0	0	5 (62.5%)	3 (37.5%)	0	
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0	
	TOTAL	298	0	26 (8.7%)	254 (85.2%)	16 (5.4%)	2 (0.7%)	

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 23/WEEK 80

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN		LOW		NORMAL		HIGH	HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	0
	LOW (50-59 BPM)	12	2 (16.7%)		4 (33.3%)		6 (50.0%)		0	0
	NORMAL (60-99 BPM)	84	0		3 (3.6%)		74 (88.1%)		7 (8.3%)	0
	HIGH (100-120 BPM)	2	0		0		1 (50.0%)		1 (50.0%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	TOTAL	98	2 (2.0%)		7 (7.1%)		81 (82.7%)		8 (8.2%)	0
SB 207499	LOW CONCERN (<50 BPM)	3	2 (66.7%)		1 (33.3%)		0		0	0
	LOW (50-59 BPM)	18	1 (5.6%)		5 (27.8%)		12 (66.7%)		0	0
	NORMAL (60-99 BPM)	166	1 (0.6%)		10 (6.0%)		148 (89.2%)		7 (4.2%)	0
	HIGH (100-120 BPM)	6	0		0		5 (83.3%)		1 (16.7%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	TOTAL	193	4 (2.1%)		16 (8.3%)		165 (85.5%)		8 (4.1%)	0
TOTAL	LOW CONCERN (<50 BPM)	3	2 (66.7%)		1 (33.3%)		0		0	0
	LOW (50-59 BPM)	30	3 (10.0%)		9 (30.0%)		18 (60.0%)		0	0
	NORMAL (60-99 BPM)	250	1 (0.4%)		13 (5.2%)		222 (88.8%)		14 (5.6%)	0
	HIGH (100-120 BPM)	8	0		0		6 (75.0%)		2 (25.0%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	TOTAL	291	6 (2.1%)		23 (7.9%)		246 (84.5%)		16 (5.5%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 24/WEEK 84

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----								
			LOW CONCERN		LOW		NORMAL		HIGH		HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	0	
	LOW (50-59 BPM)	18	1	(5.6%)	10	(55.6%)	6	(33.3%)	1	(5.6%)	0
	NORMAL (60-99 BPM)	141	0		9	(6.4%)	121	(85.8%)	11	(7.8%)	0
	HIGH (100-120 BPM)	4	0		0		3	(75.0%)	1	(25.0%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	163	1	(0.6%)	19	(11.7%)	130	(79.8%)	13	(8.0%)	0
SB 207499	LOW CONCERN (<50 BPM)	5	2	(40.0%)	2	(40.0%)	1	(20.0%)	0		0
	LOW (50-59 BPM)	45	5	(11.1%)	10	(22.2%)	29	(64.4%)	1	(2.2%)	0
	NORMAL (60-99 BPM)	274	1	(0.4%)	14	(5.1%)	247	(90.1%)	11	(4.0%)	1 (0.4%)
	HIGH (100-120 BPM)	10	0		1	(10.0%)	7	(70.0%)	2	(20.0%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	334	8	(2.4%)	27	(8.1%)	284	(85.0%)	14	(4.2%)	1 (0.3%)
TOTAL	LOW CONCERN (<50 BPM)	5	2	(40.0%)	2	(40.0%)	1	(20.0%)	0		0
	LOW (50-59 BPM)	63	6	(9.5%)	20	(31.7%)	35	(55.6%)	2	(3.2%)	0
	NORMAL (60-99 BPM)	415	1	(0.2%)	23	(5.5%)	368	(88.7%)	22	(5.3%)	1 (0.2%)
	HIGH (100-120 BPM)	14	0		1	(7.1%)	10	(71.4%)	3	(21.4%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	497	9	(1.8%)	46	(9.3%)	414	(83.3%)	27	(5.4%)	1 (0.2%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 25/WEEK 88

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN	
PLACEBO	LOW CONCERN (<50 BPM)	0	0	0	0	0	0	0
	LOW (50-59 BPM)	5	0	2 (40.0%)	3 (60.0%)	0	0	0
	NORMAL (60-99 BPM)	46	0	6 (13.0%)	37 (80.4%)	3 (6.5%)	0	0
	HIGH (100-120 BPM)	2	0	0	1 (50.0%)	1 (50.0%)	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0	0
	TOTAL	53	0	8 (15.1%)	41 (77.4%)	4 (7.5%)	0	0
SB 207499	LOW CONCERN (<50 BPM)	2	1 (50.0%)	1 (50.0%)	0	0	0	0
	LOW (50-59 BPM)	12	0	6 (50.0%)	6 (50.0%)	0	0	0
	NORMAL (60-99 BPM)	80	0	3 (3.8%)	71 (88.8%)	6 (7.5%)	0	0
	HIGH (100-120 BPM)	3	0	0	2 (66.7%)	1 (33.3%)	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0	0
	TOTAL	97	1 (1.0%)	10 (10.3%)	79 (81.4%)	7 (7.2%)	0	0
TOTAL	LOW CONCERN (<50 BPM)	2	1 (50.0%)	1 (50.0%)	0	0	0	0
	LOW (50-59 BPM)	17	0	8 (47.1%)	9 (52.9%)	0	0	0
	NORMAL (60-99 BPM)	126	0	9 (7.1%)	108 (85.7%)	9 (7.1%)	0	0
	HIGH (100-120 BPM)	5	0	0	3 (60.0%)	2 (40.0%)	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0	0
	TOTAL	150	1 (0.7%)	18 (12.0%)	120 (80.0%)	11 (7.3%)	0	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 26/WEEK 92

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN		LOW		NORMAL		HIGH	HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	0
	LOW (50-59 BPM)	5	1 (20.0%)		1 (20.0%)		3 (60.0%)		0	0
	NORMAL (60-99 BPM)	45	0		6 (13.3%)		34 (75.6%)		5 (11.1%)	0
	HIGH (100-120 BPM)	2	0		0		2 (100.0%)		0	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	TOTAL	52	1 (1.9%)		7 (13.5%)		39 (75.0%)		5 (9.6%)	0
SB 207499	LOW CONCERN (<50 BPM)	2	2 (100.0%)		0		0		0	0
	LOW (50-59 BPM)	12	0		6 (50.0%)		6 (50.0%)		0	0
	NORMAL (60-99 BPM)	79	0		3 (3.8%)		69 (87.3%)		7 (8.9%)	0
	HIGH (100-120 BPM)	3	0		0		2 (66.7%)		1 (33.3%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	TOTAL	96	2 (2.1%)		9 (9.4%)		77 (80.2%)		8 (8.3%)	0
TOTAL	LOW CONCERN (<50 BPM)	2	2 (100.0%)		0		0		0	0
	LOW (50-59 BPM)	17	1 (5.9%)		7 (41.2%)		9 (52.9%)		0	0
	NORMAL (60-99 BPM)	124	0		9 (7.3%)		103 (83.1%)		12 (9.7%)	0
	HIGH (100-120 BPM)	5	0		0		4 (80.0%)		1 (20.0%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	TOTAL	148	3 (2.0%)		16 (10.8%)		116 (78.4%)		13 (8.8%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 27/WEEK 96

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----								
			LOW CONCERN		LOW		NORMAL		HIGH		HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0		0
	LOW (50-59 BPM)	19	4	(21.1%)	6	(31.6%)	9	(47.4%)	0		0
	NORMAL (60-99 BPM)	137	0		10	(7.3%)	120	(87.6%)	7	(5.1%)	0
	HIGH (100-120 BPM)	4	0		0		3	(75.0%)	1	(25.0%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	160	4	(2.5%)	16	(10.0%)	132	(82.5%)	8	(5.0%)	0
SB 207499	LOW CONCERN (<50 BPM)	6	2	(33.3%)	4	(66.7%)	0		0		0
	LOW (50-59 BPM)	45	1	(2.2%)	13	(28.9%)	31	(68.9%)	0		0
	NORMAL (60-99 BPM)	268	0		13	(4.9%)	243	(90.7%)	11	(4.1%)	1 (0.4%)
	HIGH (100-120 BPM)	9	0		0		6	(66.7%)	3	(33.3%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	328	3	(0.9%)	30	(9.1%)	280	(85.4%)	14	(4.3%)	1 (0.3%)
TOTAL	LOW CONCERN (<50 BPM)	6	2	(33.3%)	4	(66.7%)	0		0		0
	LOW (50-59 BPM)	64	5	(7.8%)	19	(29.7%)	40	(62.5%)	0		0
	NORMAL (60-99 BPM)	405	0		23	(5.7%)	363	(89.6%)	18	(4.4%)	1 (0.2%)
	HIGH (100-120 BPM)	13	0		0		9	(69.2%)	4	(30.8%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	488	7	(1.4%)	46	(9.4%)	412	(84.4%)	22	(4.5%)	1 (0.2%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 28/WEEK 100

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN	
PLACEBO	LOW CONCERN (<50 BPM)	0	0	0	0	0	0	0
	LOW (50-59 BPM)	1	0	1 (100.0%)	0	0	0	0
	NORMAL (60-99 BPM)	21	0	2 (9.5%)	18 (85.7%)	1 (4.8%)	0	0
	HIGH (100-120 BPM)	0	0	0	0	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0	0
	TOTAL	22	0	3 (13.6%)	18 (81.8%)	1 (4.5%)	0	0
SB 207499	LOW CONCERN (<50 BPM)	1	0	0	1 (100.0%)	0	0	0
	LOW (50-59 BPM)	6	0	3 (50.0%)	3 (50.0%)	0	0	0
	NORMAL (60-99 BPM)	41	0	3 (7.3%)	36 (87.8%)	2 (4.9%)	0	0
	HIGH (100-120 BPM)	1	0	0	1 (100.0%)	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0	0
	TOTAL	49	0	6 (12.2%)	41 (83.7%)	2 (4.1%)	0	0
TOTAL	LOW CONCERN (<50 BPM)	1	0	0	1 (100.0%)	0	0	0
	LOW (50-59 BPM)	7	0	4 (57.1%)	3 (42.9%)	0	0	0
	NORMAL (60-99 BPM)	62	0	5 (8.1%)	54 (87.1%)	3 (4.8%)	0	0
	HIGH (100-120 BPM)	1	0	0	1 (100.0%)	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0	0
	TOTAL	71	0	9 (12.7%)	59 (83.1%)	3 (4.2%)	0	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 29/WEEK 104

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN	
PLACEBO	LOW CONCERN (<50 BPM)	0	0	0	0	0	0	0
	LOW (50-59 BPM)	1	0	0	1 (100.0%)	0	0	0
	NORMAL (60-99 BPM)	17	0	3 (17.6%)	12 (70.6%)	2 (11.8%)	0	0
	HIGH (100-120 BPM)	0	0	0	0	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0	0
	TOTAL	18	0	3 (16.7%)	13 (72.2%)	2 (11.1%)	0	0
SB 207499	LOW CONCERN (<50 BPM)	0	0	0	0	0	0	0
	LOW (50-59 BPM)	4	0	2 (50.0%)	2 (50.0%)	0	0	0
	NORMAL (60-99 BPM)	35	0	3 (8.6%)	29 (82.9%)	3 (8.6%)	0	0
	HIGH (100-120 BPM)	1	0	0	1 (100.0%)	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0	0
	TOTAL	40	0	5 (12.5%)	32 (80.0%)	3 (7.5%)	0	0
TOTAL	LOW CONCERN (<50 BPM)	0	0	0	0	0	0	0
	LOW (50-59 BPM)	5	0	2 (40.0%)	3 (60.0%)	0	0	0
	NORMAL (60-99 BPM)	52	0	6 (11.5%)	41 (78.8%)	5 (9.6%)	0	0
	HIGH (100-120 BPM)	1	0	0	1 (100.0%)	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0	0
	TOTAL	58	0	8 (13.8%)	45 (77.6%)	5 (8.6%)	0	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 30/WEEK 108

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----									
			LOW CONCERN		LOW		NORMAL		HIGH		HIGH CONCERN	

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0		0	
	LOW (50-59 BPM)	13	3	(23.1%)	5	(38.5%)	5	(38.5%)	0		0	
	NORMAL (60-99 BPM)	112	0		6	(5.4%)	96	(85.7%)	9	(8.0%)	1	(0.9%)
	HIGH (100-120 BPM)	1	0		0		1	(100.0%)	0		0	
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0	
	TOTAL	126	3	(2.4%)	11	(8.7%)	102	(81.0%)	9	(7.1%)	1	(0.8%)
SB 207499	LOW CONCERN (<50 BPM)	3	0		3	(100.0%)	0		0		0	
	LOW (50-59 BPM)	36	1	(2.8%)	13	(36.1%)	22	(61.1%)	0		0	
	NORMAL (60-99 BPM)	225	0		9	(4.0%)	201	(89.3%)	14	(6.2%)	1	(0.4%)
	HIGH (100-120 BPM)	8	0		0		7	(87.5%)	0		1	(12.5%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0	
	TOTAL	272	1	(0.4%)	25	(9.2%)	230	(84.6%)	14	(5.1%)	2	(0.7%)
TOTAL	LOW CONCERN (<50 BPM)	3	0		3	(100.0%)	0		0		0	
	LOW (50-59 BPM)	49	4	(8.2%)	18	(36.7%)	27	(55.1%)	0		0	
	NORMAL (60-99 BPM)	337	0		15	(4.5%)	297	(88.1%)	23	(6.8%)	2	(0.6%)
	HIGH (100-120 BPM)	9	0		0		8	(88.9%)	0		1	(11.1%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0	
	TOTAL	398	4	(1.0%)	36	(9.0%)	332	(83.4%)	23	(5.8%)	3	(0.8%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 31/WEEK 112

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<50 BPM)	0	0	0	0	0	0
	LOW (50-59 BPM)	1	0	0	1 (100.0%)	0	0
	NORMAL (60-99 BPM)	8	0	2 (25.0%)	6 (75.0%)	0	0
	HIGH (100-120 BPM)	0	0	0	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	TOTAL	9	0	2 (22.2%)	7 (77.8%)	0	0
SB 207499	LOW CONCERN (<50 BPM)	0	0	0	0	0	0
	LOW (50-59 BPM)	1	0	1 (100.0%)	0	0	0
	NORMAL (60-99 BPM)	16	0	1 (6.3%)	15 (93.8%)	0	0
	HIGH (100-120 BPM)	1	0	0	1 (100.0%)	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	TOTAL	18	0	2 (11.1%)	16 (88.9%)	0	0
TOTAL	LOW CONCERN (<50 BPM)	0	0	0	0	0	0
	LOW (50-59 BPM)	2	0	1 (50.0%)	1 (50.0%)	0	0
	NORMAL (60-99 BPM)	24	0	3 (12.5%)	21 (87.5%)	0	0
	HIGH (100-120 BPM)	1	0	0	1 (100.0%)	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	TOTAL	27	0	4 (14.8%)	23 (85.2%)	0	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 32/WEEK 116

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN	
PLACEBO	LOW CONCERN (<50 BPM)	0	0	0	0	0	0	0
	LOW (50-59 BPM)	1	0	0	1 (100.0%)	0	0	0
	NORMAL (60-99 BPM)	8	0	1 (12.5%)	7 (87.5%)	0	0	0
	HIGH (100-120 BPM)	0	0	0	0	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0	0
	TOTAL	9	0	1 (11.1%)	8 (88.9%)	0	0	0
SB 207499	LOW CONCERN (<50 BPM)	0	0	0	0	0	0	0
	LOW (50-59 BPM)	1	0	1 (100.0%)	0	0	0	0
	NORMAL (60-99 BPM)	15	0	0	13 (86.7%)	2 (13.3%)	0	0
	HIGH (100-120 BPM)	0	0	0	0	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0	0
	TOTAL	16	0	1 (6.3%)	13 (81.3%)	2 (12.5%)	0	0
TOTAL	LOW CONCERN (<50 BPM)	0	0	0	0	0	0	0
	LOW (50-59 BPM)	2	0	1 (50.0%)	1 (50.0%)	0	0	0
	NORMAL (60-99 BPM)	23	0	1 (4.3%)	20 (87.0%)	2 (8.7%)	0	0
	HIGH (100-120 BPM)	0	0	0	0	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0	0
	TOTAL	25	0	2 (8.0%)	21 (84.0%)	2 (8.0%)	0	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 33/WEEK 120

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----							
			LOW CONCERN		LOW		NORMAL		HIGH	

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0	0
	LOW (50-59 BPM)	11	1 (9.1%)		5 (45.5%)		5 (45.5%)		0	0
	NORMAL (60-99 BPM)	80	1 (1.3%)		2 (2.5%)		71 (88.8%)		6 (7.5%)	0
	HIGH (100-120 BPM)	0	0		0		0		0	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	TOTAL	91	2 (2.2%)		7 (7.7%)		76 (83.5%)		6 (6.6%)	0
SB 207499	LOW CONCERN (<50 BPM)	3	1 (33.3%)		1 (33.3%)		1 (33.3%)		0	0
	LOW (50-59 BPM)	21	0		8 (38.1%)		13 (61.9%)		0	0
	NORMAL (60-99 BPM)	158	0		11 (7.0%)		137 (86.7%)		10 (6.3%)	0
	HIGH (100-120 BPM)	5	0		0		4 (80.0%)		1 (20.0%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	TOTAL	187	1 (0.5%)		20 (10.7%)		155 (82.9%)		11 (5.9%)	0
TOTAL	LOW CONCERN (<50 BPM)	3	1 (33.3%)		1 (33.3%)		1 (33.3%)		0	0
	LOW (50-59 BPM)	32	1 (3.1%)		13 (40.6%)		18 (56.3%)		0	0
	NORMAL (60-99 BPM)	238	1 (0.4%)		13 (5.5%)		208 (87.4%)		16 (6.7%)	0
	HIGH (100-120 BPM)	5	0		0		4 (80.0%)		1 (20.0%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0	0
	TOTAL	278	3 (1.1%)		27 (9.7%)		231 (83.1%)		17 (6.1%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 34/WEEK 124

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<50 BPM)	0	0	0	0	0	0
	LOW (50-59 BPM)	0	0	0	0	0	0
	NORMAL (60-99 BPM)	3	0	1 (33.3%)	2 (66.7%)	0	0
	HIGH (100-120 BPM)	0	0	0	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	TOTAL	3	0	1 (33.3%)	2 (66.7%)	0	0
SB 207499	LOW CONCERN (<50 BPM)	0	0	0	0	0	0
	LOW (50-59 BPM)	0	0	0	0	0	0
	NORMAL (60-99 BPM)	3	0	0	3 (100.0%)	0	0
	HIGH (100-120 BPM)	0	0	0	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	TOTAL	3	0	0	3 (100.0%)	0	0
TOTAL	LOW CONCERN (<50 BPM)	0	0	0	0	0	0
	LOW (50-59 BPM)	0	0	0	0	0	0
	NORMAL (60-99 BPM)	6	0	1 (16.7%)	5 (83.3%)	0	0
	HIGH (100-120 BPM)	0	0	0	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	TOTAL	6	0	1 (16.7%)	5 (83.3%)	0	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 35/WEEK 128

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<50 BPM)	0	0	0	0	0	0
	LOW (50-59 BPM)	0	0	0	0	0	0
	NORMAL (60-99 BPM)	3	0	0	3 (100.0%)	0	0
	HIGH (100-120 BPM)	0	0	0	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	TOTAL	3	0	0	3 (100.0%)	0	0
SB 207499	LOW CONCERN (<50 BPM)	0	0	0	0	0	0
	LOW (50-59 BPM)	0	0	0	0	0	0
	NORMAL (60-99 BPM)	3	0	0	3 (100.0%)	0	0
	HIGH (100-120 BPM)	0	0	0	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	TOTAL	3	0	0	3 (100.0%)	0	0
TOTAL	LOW CONCERN (<50 BPM)	0	0	0	0	0	0
	LOW (50-59 BPM)	0	0	0	0	0	0
	NORMAL (60-99 BPM)	6	0	0	6 (100.0%)	0	0
	HIGH (100-120 BPM)	0	0	0	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	TOTAL	6	0	0	6 (100.0%)	0	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 36/WEEK 132

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----								
			LOW CONCERN		LOW		NORMAL		HIGH		HIGH CONCERN

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0		0
	LOW (50-59 BPM)	6	1	(16.7%)	1	(16.7%)	4	(66.7%)	0		0
	NORMAL (60-99 BPM)	30	0		3	(10.0%)	25	(83.3%)	2	(6.7%)	0
	HIGH (100-120 BPM)	0	0		0		0		0		0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	36	1	(2.8%)	4	(11.1%)	29	(80.6%)	2	(5.6%)	0
SB 207499	LOW CONCERN (<50 BPM)	0	0		0		0		0		0
	LOW (50-59 BPM)	6	1	(16.7%)	3	(50.0%)	2	(33.3%)	0		0
	NORMAL (60-99 BPM)	49	0		1	(2.0%)	43	(87.8%)	5	(10.2%)	0
	HIGH (100-120 BPM)	3	0		0		1	(33.3%)	2	(66.7%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	58	1	(1.7%)	4	(6.9%)	46	(79.3%)	7	(12.1%)	0
TOTAL	LOW CONCERN (<50 BPM)	0	0		0		0		0		0
	LOW (50-59 BPM)	12	2	(16.7%)	4	(33.3%)	6	(50.0%)	0		0
	NORMAL (60-99 BPM)	79	0		4	(5.1%)	68	(86.1%)	7	(8.9%)	0
	HIGH (100-120 BPM)	3	0		0		1	(33.3%)	2	(66.7%)	0
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0
	TOTAL	94	2	(2.1%)	8	(8.5%)	75	(79.8%)	9	(9.6%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: VISIT 37/WEEK 136

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			LOW CONCERN	LOW	NORMAL	HIGH	HIGH CONCERN
PLACEBO	LOW CONCERN (<50 BPM)	0	0	0	0	0	0
	LOW (50-59 BPM)	0	0	0	0	0	0
	NORMAL (60-99 BPM)	1	0	0	1 (100.0%)	0	0
	HIGH (100-120 BPM)	0	0	0	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	TOTAL	1	0	0	1 (100.0%)	0	0
SB 207499	LOW CONCERN (<50 BPM)	0	0	0	0	0	0
	LOW (50-59 BPM)	0	0	0	0	0	0
	NORMAL (60-99 BPM)	2	0	0	1 (50.0%)	1 (50.0%)	0
	HIGH (100-120 BPM)	0	0	0	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	TOTAL	2	0	0	1 (50.0%)	1 (50.0%)	0
TOTAL	LOW CONCERN (<50 BPM)	0	0	0	0	0	0
	LOW (50-59 BPM)	0	0	0	0	0	0
	NORMAL (60-99 BPM)	3	0	0	2 (66.7%)	1 (33.3%)	0
	HIGH (100-120 BPM)	0	0	0	0	0	0
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0
	TOTAL	3	0	0	2 (66.7%)	1 (33.3%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: VENTRICULAR RATE TIME POINT: TOTAL ON-THERAPY

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----									
			LOW CONCERN		LOW		NORMAL		HIGH		HIGH CONCERN	

PLACEBO	LOW CONCERN (<50 BPM)	0	0		0		0		0		0	
	LOW (50-59 BPM)	25	8	(32.0%)	12	(48.0%)	2	(8.0%)	2	(8.0%)	2	(8.0%)
	NORMAL (60-99 BPM)	207	2	(1.0%)	52	(25.1%)	105	(50.7%)	49	(23.7%)	6	(2.9%)
	HIGH (100-120 BPM)	7	0		0		1	(14.3%)	6	(85.7%)	0	
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0	
	TOTAL	239	10	(4.2%)	64	(26.8%)	108	(45.2%)	57	(23.8%)	8	(3.3%)
SB 207499	LOW CONCERN (<50 BPM)	6	5	(83.3%)	1	(16.7%)	0		1	(16.7%)	0	
	LOW (50-59 BPM)	61	14	(23.0%)	35	(57.4%)	9	(14.8%)	2	(3.3%)	3	(4.9%)
	NORMAL (60-99 BPM)	392	8	(2.0%)	91	(23.2%)	206	(52.6%)	85	(21.7%)	11	(2.8%)
	HIGH (100-120 BPM)	12	0		2	(16.7%)	0		8	(66.7%)	3	(25.0%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0	
	TOTAL	471	27	(5.7%)	129	(27.4%)	215	(45.6%)	96	(20.4%)	17	(3.6%)
TOTAL	LOW CONCERN (<50 BPM)	6	5	(83.3%)	1	(16.7%)	0		1	(16.7%)	0	
	LOW (50-59 BPM)	86	22	(25.6%)	47	(54.7%)	11	(12.8%)	4	(4.7%)	5	(5.8%)
	NORMAL (60-99 BPM)	599	10	(1.7%)	143	(23.9%)	311	(51.9%)	134	(22.4%)	17	(2.8%)
	HIGH (100-120 BPM)	19	0		2	(10.5%)	1	(5.3%)	14	(73.7%)	3	(15.8%)
	HIGH CONCERN (>120 BPM)	0	0		0		0		0		0	
	TOTAL	710	37	(5.2%)	193	(27.2%)	323	(45.5%)	153	(21.5%)	25	(3.5%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PRIOR TREATMENT	BASELINE	PARAMETER: VENTRICULAR RATE NUMBER OF PATIENTS TESTED	TIME POINT: ENDPOINT							
			-----ON-THERAPY-----		-----ON-THERAPY-----		-----ON-THERAPY-----		-----ON-THERAPY-----	
			LOW CONCERN	LOW	LOW	NORMAL	HIGH	HIGH CONCERN		
PLACEBO	LOW CONCERN (<50 BPM)	0	0	0	0	0	0	0	0	0
	LOW (50-59 BPM)	25	3 (12.0%)	8 (32.0%)	12 (48.0%)	1 (4.0%)	1 (4.0%)	1 (4.0%)		
	NORMAL (60-99 BPM)	207	0	10 (4.8%)	183 (88.4%)	13 (6.3%)	1 (0.5%)			
	HIGH (100-120 BPM)	7	0	0	5 (71.4%)	2 (28.6%)	0			
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0	0		
	TOTAL	239	3 (1.3%)	18 (7.5%)	200 (83.7%)	16 (6.7%)	2 (0.8%)			
SB 207499	LOW CONCERN (<50 BPM)	6	2 (33.3%)	2 (33.3%)	2 (33.3%)	0	0	0		
	LOW (50-59 BPM)	61	2 (3.3%)	20 (32.8%)	38 (62.3%)	1 (1.6%)	0			
	NORMAL (60-99 BPM)	392	0	19 (4.8%)	350 (89.3%)	22 (5.6%)	1 (0.3%)			
	HIGH (100-120 BPM)	12	0	0	7 (58.3%)	4 (33.3%)	1 (8.3%)			
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0			
	TOTAL	471	4 (0.8%)	41 (8.7%)	397 (84.3%)	27 (5.7%)	2 (0.4%)			
TOTAL	LOW CONCERN (<50 BPM)	6	2 (33.3%)	2 (33.3%)	2 (33.3%)	0	0			
	LOW (50-59 BPM)	86	5 (5.8%)	28 (32.6%)	50 (58.1%)	2 (2.3%)	1 (1.2%)			
	NORMAL (60-99 BPM)	599	0	29 (4.8%)	533 (89.0%)	35 (5.8%)	2 (0.3%)			
	HIGH (100-120 BPM)	19	0	0	12 (63.2%)	6 (31.6%)	1 (5.3%)			
	HIGH CONCERN (>120 BPM)	0	0	0	0	0	0			
	TOTAL	710	7 (1.0%)	59 (8.3%)	597 (84.1%)	43 (6.1%)	4 (0.6%)			

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 2/WEEK 1

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<200 MSEC)	214	210	(98.1%)	4	(1.9%)	0
	HIGH (200-249 MSEC)	11	3	(27.3%)	8	(72.7%)	0
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	2	2	(100.0%)	0		0
	TOTAL	228	215	(94.3%)	12	(5.3%)	1 (0.4%)
SB 207499	NORMAL (<200 MSEC)	421	409	(97.1%)	12	(2.9%)	0
	HIGH (200-249 MSEC)	26	7	(26.9%)	17	(65.4%)	2 (7.7%)
	CONCERN (>=250 MSEC)	2	0		1	(50.0%)	1 (50.0%)
	MISSING	2	1	(50.0%)	1	(50.0%)	0
	TOTAL	451	417	(92.5%)	31	(6.9%)	3 (0.7%)
TOTAL	NORMAL (<200 MSEC)	635	619	(97.5%)	16	(2.5%)	0
	HIGH (200-249 MSEC)	37	10	(27.0%)	25	(67.6%)	2 (5.4%)
	CONCERN (>=250 MSEC)	3	0		1	(33.3%)	2 (66.7%)
	MISSING	4	3	(75.0%)	1	(25.0%)	0
	TOTAL	679	632	(93.1%)	43	(6.3%)	4 (0.6%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 3/WEEK 2

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<200 MSEC)	205	201	(98.0%)	4	(2.0%)	0
	HIGH (200-249 MSEC)	11	5	(45.5%)	6	(54.5%)	0
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	1	1	(100.0%)	0		0
	TOTAL	218	207	(95.0%)	10	(4.6%)	1 (0.5%)
SB 207499	NORMAL (<200 MSEC)	413	402	(97.3%)	11	(2.7%)	0
	HIGH (200-249 MSEC)	25	8	(32.0%)	14	(56.0%)	3 (12.0%)
	CONCERN (>=250 MSEC)	2	0		1	(50.0%)	1 (50.0%)
	MISSING	2	1	(50.0%)	1	(50.0%)	0
	TOTAL	442	411	(93.0%)	27	(6.1%)	4 (0.9%)
TOTAL	NORMAL (<200 MSEC)	618	603	(97.6%)	15	(2.4%)	0
	HIGH (200-249 MSEC)	36	13	(36.1%)	20	(55.6%)	3 (8.3%)
	CONCERN (>=250 MSEC)	3	0		1	(33.3%)	2 (66.7%)
	MISSING	3	2	(66.7%)	1	(33.3%)	0
	TOTAL	660	618	(93.6%)	37	(5.6%)	5 (0.8%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 4/WEEK 4

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<200 MSEC)	197	194	(98.5%)	3	(1.5%)	0
	HIGH (200-249 MSEC)	10	6	(60.0%)	4	(40.0%)	0
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	1	1	(100.0%)	0		0
	TOTAL	209	201	(96.2%)	7	(3.3%)	1 (0.5%)
SB 207499	NORMAL (<200 MSEC)	419	407	(97.1%)	12	(2.9%)	0
	HIGH (200-249 MSEC)	26	8	(30.8%)	16	(61.5%)	2 (7.7%)
	CONCERN (>=250 MSEC)	2	0		0		2 (100.0%)
	MISSING	2	1	(50.0%)	1	(50.0%)	0
	TOTAL	449	416	(92.7%)	29	(6.5%)	4 (0.9%)
TOTAL	NORMAL (<200 MSEC)	616	601	(97.6%)	15	(2.4%)	0
	HIGH (200-249 MSEC)	36	14	(38.9%)	20	(55.6%)	2 (5.6%)
	CONCERN (>=250 MSEC)	3	0		0		3 (100.0%)
	MISSING	3	2	(66.7%)	1	(33.3%)	0
	TOTAL	658	617	(93.8%)	36	(5.5%)	5 (0.8%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 5/WEEK 8

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<200 MSEC)	196	194	(99.0%)	2	(1.0%)	0
	HIGH (200-249 MSEC)	10	5	(50.0%)	5	(50.0%)	0
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	2	2	(100.0%)	0		0
	TOTAL	209	201	(96.2%)	7	(3.3%)	1 (0.5%)
SB 207499	NORMAL (<200 MSEC)	407	400	(98.3%)	7	(1.7%)	0
	HIGH (200-249 MSEC)	26	6	(23.1%)	16	(61.5%)	4 (15.4%)
	CONCERN (>=250 MSEC)	2	0		0		2 (100.0%)
	MISSING	2	1	(50.0%)	1	(50.0%)	0
	TOTAL	437	407	(93.1%)	24	(5.5%)	6 (1.4%)
TOTAL	NORMAL (<200 MSEC)	603	594	(98.5%)	9	(1.5%)	0
	HIGH (200-249 MSEC)	36	11	(30.6%)	21	(58.3%)	4 (11.1%)
	CONCERN (>=250 MSEC)	3	0		0		3 (100.0%)
	MISSING	4	3	(75.0%)	1	(25.0%)	0
	TOTAL	646	608	(94.1%)	31	(4.8%)	7 (1.1%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 6/WEEK 12

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<200 MSEC)	192	189	(98.4%)	3	(1.6%)	0
	HIGH (200-249 MSEC)	10	5	(50.0%)	5	(50.0%)	0
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	1	0		1	(100.0%)	0
	TOTAL	204	194	(95.1%)	9	(4.4%)	1 (0.5%)
SB 207499	NORMAL (<200 MSEC)	407	392	(96.3%)	15	(3.7%)	0
	HIGH (200-249 MSEC)	25	7	(28.0%)	15	(60.0%)	3 (12.0%)
	CONCERN (>=250 MSEC)	2	0		0		2 (100.0%)
	MISSING	1	1	(100.0%)	0		0
	TOTAL	435	400	(92.0%)	30	(6.9%)	5 (1.1%)
TOTAL	NORMAL (<200 MSEC)	599	581	(97.0%)	18	(3.0%)	0
	HIGH (200-249 MSEC)	35	12	(34.3%)	20	(57.1%)	3 (8.6%)
	CONCERN (>=250 MSEC)	3	0		0		3 (100.0%)
	MISSING	2	1	(50.0%)	1	(50.0%)	0
	TOTAL	639	594	(93.0%)	39	(6.1%)	6 (0.9%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 7/WEEK 16

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		HIGH	CONCERN
PLACEBO	NORMAL (<200 MSEC)	184	184	(100.0%)	0	0
	HIGH (200-249 MSEC)	10	2	(20.0%)	8	0
	CONCERN (>=250 MSEC)	1	0		0	1 (100.0%)
	MISSING	0	0		0	0
	TOTAL	195	186	(95.4%)	8	1 (0.5%)
SB 207499	NORMAL (<200 MSEC)	399	389	(97.5%)	10	0
	HIGH (200-249 MSEC)	25	7	(28.0%)	16	2 (8.0%)
	CONCERN (>=250 MSEC)	1	0		0	1 (100.0%)
	MISSING	2	1	(50.0%)	1	0
	TOTAL	427	397	(93.0%)	27	3 (0.7%)
TOTAL	NORMAL (<200 MSEC)	583	573	(98.3%)	10	0
	HIGH (200-249 MSEC)	35	9	(25.7%)	24	2 (5.7%)
	CONCERN (>=250 MSEC)	2	0		0	2 (100.0%)
	MISSING	2	1	(50.0%)	1	0
	TOTAL	622	583	(93.7%)	35	4 (0.6%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 8/WEEK 20

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<200 MSEC)	180	178	(98.9%)	2	(1.1%)	0
	HIGH (200-249 MSEC)	10	4	(40.0%)	6	(60.0%)	0
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	1	1	(100.0%)	0		0
	TOTAL	192	183	(95.3%)	8	(4.2%)	1 (0.5%)
SB 207499	NORMAL (<200 MSEC)	397	388	(97.7%)	9	(2.3%)	0
	HIGH (200-249 MSEC)	25	7	(28.0%)	16	(64.0%)	2 (8.0%)
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	2	1	(50.0%)	0		1 (50.0%)
	TOTAL	425	396	(93.2%)	25	(5.9%)	4 (0.9%)
TOTAL	NORMAL (<200 MSEC)	577	566	(98.1%)	11	(1.9%)	0
	HIGH (200-249 MSEC)	35	11	(31.4%)	22	(62.9%)	2 (5.7%)
	CONCERN (>=250 MSEC)	2	0		0		2 (100.0%)
	MISSING	3	2	(66.7%)	0		1 (33.3%)
	TOTAL	617	579	(93.8%)	33	(5.3%)	5 (0.8%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 9/WEEK 24

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<200 MSEC)	175	175	(100.0%)	0		0
	HIGH (200-249 MSEC)	10	7	(70.0%)	3	(30.0%)	0
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	1	1	(100.0%)	0		0
	TOTAL	187	183	(97.9%)	3	(1.6%)	1 (0.5%)
SB 207499	NORMAL (<200 MSEC)	393	383	(97.5%)	10	(2.5%)	0
	HIGH (200-249 MSEC)	23	3	(13.0%)	19	(82.6%)	1 (4.3%)
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	2	1	(50.0%)	1	(50.0%)	0
	TOTAL	419	387	(92.4%)	30	(7.2%)	2 (0.5%)
TOTAL	NORMAL (<200 MSEC)	568	558	(98.2%)	10	(1.8%)	0
	HIGH (200-249 MSEC)	33	10	(30.3%)	22	(66.7%)	1 (3.0%)
	CONCERN (>=250 MSEC)	2	0		0		2 (100.0%)
	MISSING	3	2	(66.7%)	1	(33.3%)	0
	TOTAL	606	570	(94.1%)	33	(5.4%)	3 (0.5%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 10/WEEK 28

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<200 MSEC)	175	172	(98.3%)	3	(1.7%)	0
	HIGH (200-249 MSEC)	9	5	(55.6%)	4	(44.4%)	0
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	1	1	(100.0%)	0		0
	TOTAL	186	178	(95.7%)	7	(3.8%)	1 (0.5%)
SB 207499	NORMAL (<200 MSEC)	392	382	(97.4%)	10	(2.6%)	0
	HIGH (200-249 MSEC)	19	4	(21.1%)	14	(73.7%)	1 (5.3%)
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	2	1	(50.0%)	0		1 (50.0%)
	TOTAL	414	387	(93.5%)	24	(5.8%)	3 (0.7%)
TOTAL	NORMAL (<200 MSEC)	567	554	(97.7%)	13	(2.3%)	0
	HIGH (200-249 MSEC)	28	9	(32.1%)	18	(64.3%)	1 (3.6%)
	CONCERN (>=250 MSEC)	2	0		0		2 (100.0%)
	MISSING	3	2	(66.7%)	0		1 (33.3%)
	TOTAL	600	565	(94.2%)	31	(5.2%)	4 (0.7%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 11/WEEK 32

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<200 MSEC)	170	169	(99.4%)	1	(0.6%)	0
	HIGH (200-249 MSEC)	9	5	(55.6%)	4	(44.4%)	0
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	2	2	(100.0%)	0		0
	TOTAL	182	176	(96.7%)	5	(2.7%)	1 (0.5%)
SB 207499	NORMAL (<200 MSEC)	388	380	(97.9%)	8	(2.1%)	0
	HIGH (200-249 MSEC)	18	3	(16.7%)	14	(77.8%)	1 (5.6%)
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	2	1	(50.0%)	0		1 (50.0%)
	TOTAL	409	384	(93.9%)	22	(5.4%)	3 (0.7%)
TOTAL	NORMAL (<200 MSEC)	558	549	(98.4%)	9	(1.6%)	0
	HIGH (200-249 MSEC)	27	8	(29.6%)	18	(66.7%)	1 (3.7%)
	CONCERN (>=250 MSEC)	2	0		0		2 (100.0%)
	MISSING	4	3	(75.0%)	0		1 (25.0%)
	TOTAL	591	560	(94.8%)	27	(4.6%)	4 (0.7%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 12/WEEK 36

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		HIGH	CONCERN
PLACEBO	NORMAL (<200 MSEC)	171	171	(100.0%)	0	0
	HIGH (200-249 MSEC)	9	3	(33.3%)	6	0
	CONCERN (>=250 MSEC)	1	0		0	1 (100.0%)
	MISSING	1	0		1 (100.0%)	0
	TOTAL	182	174	(95.6%)	7	1 (0.5%)
SB 207499	NORMAL (<200 MSEC)	378	372	(98.4%)	6	0
	HIGH (200-249 MSEC)	20	4	(20.0%)	15	1 (5.0%)
	CONCERN (>=250 MSEC)	1	0		0	1 (100.0%)
	MISSING	2	1	(50.0%)	1	0
	TOTAL	401	377	(94.0%)	22	2 (0.5%)
TOTAL	NORMAL (<200 MSEC)	549	543	(98.9%)	6	0
	HIGH (200-249 MSEC)	29	7	(24.1%)	21	1 (3.4%)
	CONCERN (>=250 MSEC)	2	0		0	2 (100.0%)
	MISSING	3	1	(33.3%)	2	0
	TOTAL	583	551	(94.5%)	29	3 (0.5%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 13/WEEK 40

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<200 MSEC)	170	169	(99.4%)	1	(0.6%)	0
	HIGH (200-249 MSEC)	9	3	(33.3%)	6	(66.7%)	0
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	1	0		1	(100.0%)	0
	TOTAL	181	172	(95.0%)	8	(4.4%)	1 (0.6%)
SB 207499	NORMAL (<200 MSEC)	374	368	(98.4%)	6	(1.6%)	0
	HIGH (200-249 MSEC)	20	5	(25.0%)	14	(70.0%)	1 (5.0%)
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	2	1	(50.0%)	0		1 (50.0%)
	TOTAL	397	374	(94.2%)	20	(5.0%)	3 (0.8%)
TOTAL	NORMAL (<200 MSEC)	544	537	(98.7%)	7	(1.3%)	0
	HIGH (200-249 MSEC)	29	8	(27.6%)	20	(69.0%)	1 (3.4%)
	CONCERN (>=250 MSEC)	2	0		0		2 (100.0%)
	MISSING	3	1	(33.3%)	1	(33.3%)	1 (33.3%)
	TOTAL	578	546	(94.5%)	28	(4.8%)	4 (0.7%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 14/WEEK 44

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		HIGH	CONCERN
PLACEBO	NORMAL (<200 MSEC)	168	168	(100.0%)	0	0
	HIGH (200-249 MSEC)	9	5	(55.6%)	4	0
	CONCERN (>=250 MSEC)	1	0		0	1 (100.0%)
	MISSING	1	0		1 (100.0%)	0
	TOTAL	179	173	(96.6%)	5	1 (0.6%)
SB 207499	NORMAL (<200 MSEC)	372	366	(98.4%)	6	0
	HIGH (200-249 MSEC)	20	4	(20.0%)	15	1 (5.0%)
	CONCERN (>=250 MSEC)	1	0		0	1 (100.0%)
	MISSING	1	0		1 (100.0%)	0
	TOTAL	394	370	(93.9%)	22	2 (0.5%)
TOTAL	NORMAL (<200 MSEC)	540	534	(98.9%)	6	0
	HIGH (200-249 MSEC)	29	9	(31.0%)	19	1 (3.4%)
	CONCERN (>=250 MSEC)	2	0		0	2 (100.0%)
	MISSING	2	0		2 (100.0%)	0
	TOTAL	573	543	(94.8%)	27	3 (0.5%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 15/WEEK 48

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<200 MSEC)	167	166	(99.4%)	1	(0.6%)	0
	HIGH (200-249 MSEC)	9	3	(33.3%)	6	(66.7%)	0
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	1	0		1	(100.0%)	0
	TOTAL	178	169	(94.9%)	8	(4.5%)	1 (0.6%)
SB 207499	NORMAL (<200 MSEC)	366	358	(97.8%)	8	(2.2%)	0
	HIGH (200-249 MSEC)	20	6	(30.0%)	13	(65.0%)	1 (5.0%)
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	1	0		1	(100.0%)	0
	TOTAL	388	364	(93.8%)	22	(5.7%)	2 (0.5%)
TOTAL	NORMAL (<200 MSEC)	533	524	(98.3%)	9	(1.7%)	0
	HIGH (200-249 MSEC)	29	9	(31.0%)	19	(65.5%)	1 (3.4%)
	CONCERN (>=250 MSEC)	2	0		0		2 (100.0%)
	MISSING	2	0		2	(100.0%)	0
	TOTAL	566	533	(94.2%)	30	(5.3%)	3 (0.5%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 16/WEEK 52

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<200 MSEC)	165	162	(98.2%)	3	(1.8%)	0
	HIGH (200-249 MSEC)	9	3	(33.3%)	6	(66.7%)	0
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	1	0		1	(100.0%)	0
	TOTAL	176	165	(93.8%)	10	(5.7%)	1 (0.6%)
SB 207499	NORMAL (<200 MSEC)	350	338	(96.6%)	12	(3.4%)	0
	HIGH (200-249 MSEC)	19	4	(21.1%)	14	(73.7%)	1 (5.3%)
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	1	0		1	(100.0%)	0
	TOTAL	371	342	(92.2%)	27	(7.3%)	2 (0.5%)
TOTAL	NORMAL (<200 MSEC)	515	500	(97.1%)	15	(2.9%)	0
	HIGH (200-249 MSEC)	28	7	(25.0%)	20	(71.4%)	1 (3.6%)
	CONCERN (>=250 MSEC)	2	0		0		2 (100.0%)
	MISSING	2	0		2	(100.0%)	0
	TOTAL	547	507	(92.7%)	37	(6.8%)	3 (0.5%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 17/WEEK 56

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<200 MSEC)	155	153	(98.7%)	2	(1.3%)	0
	HIGH (200-249 MSEC)	8	3	(37.5%)	5	(62.5%)	0
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	1	0		1	(100.0%)	0
	TOTAL	165	156	(94.5%)	8	(4.8%)	1 (0.6%)
SB 207499	NORMAL (<200 MSEC)	333	325	(97.6%)	8	(2.4%)	0
	HIGH (200-249 MSEC)	20	4	(20.0%)	14	(70.0%)	2 (10.0%)
	CONCERN (>=250 MSEC)	0	0		0		0
	MISSING	1	0		1	(100.0%)	0
	TOTAL	354	329	(92.9%)	23	(6.5%)	2 (0.6%)
TOTAL	NORMAL (<200 MSEC)	488	478	(98.0%)	10	(2.0%)	0
	HIGH (200-249 MSEC)	28	7	(25.0%)	19	(67.9%)	2 (7.1%)
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	2	0		2	(100.0%)	0
	TOTAL	519	485	(93.4%)	31	(6.0%)	3 (0.6%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 18/WEEK 60

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<200 MSEC)	160	157	(98.1%)	3	(1.9%)	0
	HIGH (200-249 MSEC)	8	4	(50.0%)	4	(50.0%)	0
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	1	0		1	(100.0%)	0
	TOTAL	170	161	(94.7%)	8	(4.7%)	1 (0.6%)
SB 207499	NORMAL (<200 MSEC)	344	336	(97.7%)	8	(2.3%)	0
	HIGH (200-249 MSEC)	19	4	(21.1%)	14	(73.7%)	1 (5.3%)
	CONCERN (>=250 MSEC)	0	0		0		0
	MISSING	1	0		1	(100.0%)	0
	TOTAL	364	340	(93.4%)	23	(6.3%)	1 (0.3%)
TOTAL	NORMAL (<200 MSEC)	504	493	(97.8%)	11	(2.2%)	0
	HIGH (200-249 MSEC)	27	8	(29.6%)	18	(66.7%)	1 (3.7%)
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	2	0		2	(100.0%)	0
	TOTAL	534	501	(93.8%)	31	(5.8%)	2 (0.4%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 19/WEEK 64

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<200 MSEC)	132	130	(98.5%)	2	(1.5%)	0
	HIGH (200-249 MSEC)	6	2	(33.3%)	4	(66.7%)	0
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	1	1	(100.0%)	0		0
	TOTAL	140	133	(95.0%)	6	(4.3%)	1 (0.7%)
SB 207499	NORMAL (<200 MSEC)	282	271	(96.1%)	11	(3.9%)	0
	HIGH (200-249 MSEC)	16	5	(31.3%)	10	(62.5%)	1 (6.3%)
	CONCERN (>=250 MSEC)	0	0		0		0
	MISSING	1	0		1	(100.0%)	0
	TOTAL	299	276	(92.3%)	22	(7.4%)	1 (0.3%)
TOTAL	NORMAL (<200 MSEC)	414	401	(96.9%)	13	(3.1%)	0
	HIGH (200-249 MSEC)	22	7	(31.8%)	14	(63.6%)	1 (4.5%)
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	2	1	(50.0%)	1	(50.0%)	0
	TOTAL	439	409	(93.2%)	28	(6.4%)	2 (0.5%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

SB 207499

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 20/WEEK 68

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<200 MSEC)	130	127	(97.7%)	3	(2.3%)	0
	HIGH (200-249 MSEC)	4	3	(75.0%)	1	(25.0%)	0
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	0	0		0		0
	TOTAL	135	130	(96.3%)	4	(3.0%)	1 (0.7%)
SB 207499	NORMAL (<200 MSEC)	271	262	(96.7%)	9	(3.3%)	0
	HIGH (200-249 MSEC)	14	4	(28.6%)	8	(57.1%)	2 (14.3%)
	CONCERN (>=250 MSEC)	0	0		0		0
	MISSING	1	0		1	(100.0%)	0
	TOTAL	286	266	(93.0%)	18	(6.3%)	2 (0.7%)
TOTAL	NORMAL (<200 MSEC)	401	389	(97.0%)	12	(3.0%)	0
	HIGH (200-249 MSEC)	18	7	(38.9%)	9	(50.0%)	2 (11.1%)
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	1	0		1	(100.0%)	0
	TOTAL	421	396	(94.1%)	22	(5.2%)	3 (0.7%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 21/WEEK 72

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<200 MSEC)	159	154	(96.9%)	5	(3.1%)	0
	HIGH (200-249 MSEC)	6	4	(66.7%)	2	(33.3%)	0
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	1	0		1	(100.0%)	0
	TOTAL	167	158	(94.6%)	8	(4.8%)	1 (0.6%)
SB 207499	NORMAL (<200 MSEC)	326	315	(96.6%)	11	(3.4%)	0
	HIGH (200-249 MSEC)	19	5	(26.3%)	13	(68.4%)	1 (5.3%)
	CONCERN (>=250 MSEC)	0	0		0		0
	MISSING	1	0		1	(100.0%)	0
	TOTAL	346	320	(92.5%)	25	(7.2%)	1 (0.3%)
TOTAL	NORMAL (<200 MSEC)	485	469	(96.7%)	16	(3.3%)	0
	HIGH (200-249 MSEC)	25	9	(36.0%)	15	(60.0%)	1 (4.0%)
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	2	0		2	(100.0%)	0
	TOTAL	513	478	(93.2%)	33	(6.4%)	2 (0.4%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 22/WEEK 76

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<200 MSEC)	93	91	(97.8%)	2	(2.2%)	0
	HIGH (200-249 MSEC)	4	3	(75.0%)	1	(25.0%)	0
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	0	0		0		0
	TOTAL	98	94	(95.9%)	3	(3.1%)	1 (1.0%)
SB 207499	NORMAL (<200 MSEC)	180	177	(98.3%)	3	(1.7%)	0
	HIGH (200-249 MSEC)	10	4	(40.0%)	4	(40.0%)	2 (20.0%)
	CONCERN (>=250 MSEC)	0	0		0		0
	MISSING	0	0		0		0
	TOTAL	190	181	(95.3%)	7	(3.7%)	2 (1.1%)
TOTAL	NORMAL (<200 MSEC)	273	268	(98.2%)	5	(1.8%)	0
	HIGH (200-249 MSEC)	14	7	(50.0%)	5	(35.7%)	2 (14.3%)
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	0	0		0		0
	TOTAL	288	275	(95.5%)	10	(3.5%)	3 (1.0%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 23/WEEK 80

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<200 MSEC)	90	88	(97.8%)	2	(2.2%)	0
	HIGH (200-249 MSEC)	4	3	(75.0%)	1	(25.0%)	0
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	0	0		0		0
	TOTAL	95	91	(95.8%)	3	(3.2%)	1 (1.1%)
SB 207499	NORMAL (<200 MSEC)	176	175	(99.4%)	1	(0.6%)	0
	HIGH (200-249 MSEC)	10	3	(30.0%)	4	(40.0%)	3 (30.0%)
	CONCERN (>=250 MSEC)	0	0		0		0
	MISSING	1	1	(100.0%)	0		0
	TOTAL	187	179	(95.7%)	5	(2.7%)	3 (1.6%)
TOTAL	NORMAL (<200 MSEC)	266	263	(98.9%)	3	(1.1%)	0
	HIGH (200-249 MSEC)	14	6	(42.9%)	5	(35.7%)	3 (21.4%)
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	1	1	(100.0%)	0		0
	TOTAL	282	270	(95.7%)	8	(2.8%)	4 (1.4%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 24/WEEK 84

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<200 MSEC)	153	150	(98.0%)	3	(2.0%)	0
	HIGH (200-249 MSEC)	5	3	(60.0%)	2	(40.0%)	0
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	1	0		1	(100.0%)	0
	TOTAL	160	153	(95.6%)	6	(3.8%)	1 (0.6%)
SB 207499	NORMAL (<200 MSEC)	306	293	(95.8%)	12	(3.9%)	1 (0.3%)
	HIGH (200-249 MSEC)	17	5	(29.4%)	10	(58.8%)	2 (11.8%)
	CONCERN (>=250 MSEC)	0	0		0		0
	MISSING	1	0		0		1 (100.0%)
	TOTAL	324	298	(92.0%)	22	(6.8%)	4 (1.2%)
TOTAL	NORMAL (<200 MSEC)	459	443	(96.5%)	15	(3.3%)	1 (0.2%)
	HIGH (200-249 MSEC)	22	8	(36.4%)	12	(54.5%)	2 (9.1%)
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	2	0		1	(50.0%)	1 (50.0%)
	TOTAL	484	451	(93.2%)	28	(5.8%)	5 (1.0%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 25/WEEK 88

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<200 MSEC)	48	46	(95.8%)	2	(4.2%)	0
	HIGH (200-249 MSEC)	1	1	(100.0%)	0		0
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	0	0		0		0
	TOTAL	50	47	(94.0%)	2	(4.0%)	1 (2.0%)
SB 207499	NORMAL (<200 MSEC)	85	83	(97.6%)	2	(2.4%)	0
	HIGH (200-249 MSEC)	7	2	(28.6%)	3	(42.9%)	2 (28.6%)
	CONCERN (>=250 MSEC)	0	0		0		0
	MISSING	0	0		0		0
	TOTAL	92	85	(92.4%)	5	(5.4%)	2 (2.2%)
TOTAL	NORMAL (<200 MSEC)	133	129	(97.0%)	4	(3.0%)	0
	HIGH (200-249 MSEC)	8	3	(37.5%)	3	(37.5%)	2 (25.0%)
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	0	0		0		0
	TOTAL	142	132	(93.0%)	7	(4.9%)	3 (2.1%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 26/WEEK 92

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<200 MSEC)	47	46	(97.9%)	1	(2.1%)	0
	HIGH (200-249 MSEC)	1	1	(100.0%)	0		0
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	0	0		0		0
	TOTAL	49	47	(95.9%)	1	(2.0%)	1 (2.0%)
SB 207499	NORMAL (<200 MSEC)	84	83	(98.8%)	1	(1.2%)	0
	HIGH (200-249 MSEC)	7	2	(28.6%)	3	(42.9%)	2 (28.6%)
	CONCERN (>=250 MSEC)	0	0		0		0
	MISSING	0	0		0		0
	TOTAL	91	85	(93.4%)	4	(4.4%)	2 (2.2%)
TOTAL	NORMAL (<200 MSEC)	131	129	(98.5%)	2	(1.5%)	0
	HIGH (200-249 MSEC)	8	3	(37.5%)	3	(37.5%)	2 (25.0%)
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	0	0		0		0
	TOTAL	140	132	(94.3%)	5	(3.6%)	3 (2.1%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 27/WEEK 96

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<200 MSEC)	150	145	(96.7%)	5	(3.3%)	0
	HIGH (200-249 MSEC)	5	4	(80.0%)	1	(20.0%)	0
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	1	0		1	(100.0%)	0
	TOTAL	157	149	(94.9%)	7	(4.5%)	1 (0.6%)
SB 207499	NORMAL (<200 MSEC)	301	290	(96.3%)	11	(3.7%)	0
	HIGH (200-249 MSEC)	17	6	(35.3%)	9	(52.9%)	2 (11.8%)
	CONCERN (>=250 MSEC)	0	0		0		0
	MISSING	1	0		1	(100.0%)	0
	TOTAL	319	296	(92.8%)	21	(6.6%)	2 (0.6%)
TOTAL	NORMAL (<200 MSEC)	451	435	(96.5%)	16	(3.5%)	0
	HIGH (200-249 MSEC)	22	10	(45.5%)	10	(45.5%)	2 (9.1%)
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	2	0		2	(100.0%)	0
	TOTAL	476	445	(93.5%)	28	(5.9%)	3 (0.6%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 28/WEEK 100

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		HIGH	CONCERN
PLACEBO	NORMAL (<200 MSEC)	20	20	(100.0%)	0	0
	HIGH (200-249 MSEC)	0	0		0	0
	CONCERN (>=250 MSEC)	1	0		0	1 (100.0%)
	MISSING	0	0		0	0
	TOTAL	21	20	(95.2%)	0	1 (4.8%)
SB 207499	NORMAL (<200 MSEC)	44	44	(100.0%)	0	0
	HIGH (200-249 MSEC)	3	1	(33.3%)	1 (33.3%)	1 (33.3%)
	CONCERN (>=250 MSEC)	0	0		0	0
	MISSING	0	0		0	0
	TOTAL	47	45	(95.7%)	1 (2.1%)	1 (2.1%)
TOTAL	NORMAL (<200 MSEC)	64	64	(100.0%)	0	0
	HIGH (200-249 MSEC)	3	1	(33.3%)	1 (33.3%)	1 (33.3%)
	CONCERN (>=250 MSEC)	1	0		0	1 (100.0%)
	MISSING	0	0		0	0
	TOTAL	68	65	(95.6%)	1 (1.5%)	2 (2.9%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 29/WEEK 104

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		HIGH	CONCERN
PLACEBO	NORMAL (<200 MSEC)	17	17	(100.0%)	0	0
	HIGH (200-249 MSEC)	0	0		0	0
	CONCERN (>=250 MSEC)	1	0		0	1 (100.0%)
	MISSING	0	0		0	0
	TOTAL	18	17	(94.4%)	0	1 (5.6%)
SB 207499	NORMAL (<200 MSEC)	36	36	(100.0%)	0	0
	HIGH (200-249 MSEC)	3	1	(33.3%)	1 (33.3%)	1 (33.3%)
	CONCERN (>=250 MSEC)	0	0		0	0
	MISSING	0	0		0	0
	TOTAL	39	37	(94.9%)	1 (2.6%)	1 (2.6%)
TOTAL	NORMAL (<200 MSEC)	53	53	(100.0%)	0	0
	HIGH (200-249 MSEC)	3	1	(33.3%)	1 (33.3%)	1 (33.3%)
	CONCERN (>=250 MSEC)	1	0		0	1 (100.0%)
	MISSING	0	0		0	0
	TOTAL	57	54	(94.7%)	1 (1.8%)	2 (3.5%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 30/WEEK 108

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<200 MSEC)	117	114	(97.4%)	3	(2.6%)	0
	HIGH (200-249 MSEC)	4	3	(75.0%)	1	(25.0%)	0
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	1	0		1	(100.0%)	0
	TOTAL	123	117	(95.1%)	5	(4.1%)	1 (0.8%)
SB 207499	NORMAL (<200 MSEC)	243	237	(97.5%)	6	(2.5%)	0
	HIGH (200-249 MSEC)	17	4	(23.5%)	11	(64.7%)	2 (11.8%)
	CONCERN (>=250 MSEC)	0	0		0		0
	MISSING	1	0		0		1 (100.0%)
	TOTAL	261	241	(92.3%)	17	(6.5%)	3 (1.1%)
TOTAL	NORMAL (<200 MSEC)	360	351	(97.5%)	9	(2.5%)	0
	HIGH (200-249 MSEC)	21	7	(33.3%)	12	(57.1%)	2 (9.5%)
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	2	0		1	(50.0%)	1 (50.0%)
	TOTAL	384	358	(93.2%)	22	(5.7%)	4 (1.0%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 31/WEEK 112

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL	HIGH	CONCERN	
PLACEBO	NORMAL (<200 MSEC)	8	8 (100.0%)	0	0	
	HIGH (200-249 MSEC)	0	0	0	0	
	CONCERN (>=250 MSEC)	1	0	0	1 (100.0%)	
	MISSING	0	0	0	0	
	TOTAL	9	8 (88.9%)	0	1 (11.1%)	
SB 207499	NORMAL (<200 MSEC)	16	16 (100.0%)	0	0	
	HIGH (200-249 MSEC)	2	0	1 (50.0%)	1 (50.0%)	
	CONCERN (>=250 MSEC)	0	0	0	0	
	MISSING	0	0	0	0	
	TOTAL	18	16 (88.9%)	1 (5.6%)	1 (5.6%)	
TOTAL	NORMAL (<200 MSEC)	24	24 (100.0%)	0	0	
	HIGH (200-249 MSEC)	2	0	1 (50.0%)	1 (50.0%)	
	CONCERN (>=250 MSEC)	1	0	0	1 (100.0%)	
	MISSING	0	0	0	0	
	TOTAL	27	24 (88.9%)	1 (3.7%)	2 (7.4%)	

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 32/WEEK 116

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL	HIGH	CONCERN	
PLACEBO	NORMAL (<200 MSEC)	8	8 (100.0%)	0	0	
	HIGH (200-249 MSEC)	0	0	0	0	
	CONCERN (>=250 MSEC)	1	0	0	1 (100.0%)	
	MISSING	0	0	0	0	
	TOTAL	9	8 (88.9%)	0	1 (11.1%)	
SB 207499	NORMAL (<200 MSEC)	14	14 (100.0%)	0	0	
	HIGH (200-249 MSEC)	1	0	1 (100.0%)	0	
	CONCERN (>=250 MSEC)	0	0	0	0	
	MISSING	0	0	0	0	
	TOTAL	15	14 (93.3%)	1 (6.7%)	0	
TOTAL	NORMAL (<200 MSEC)	22	22 (100.0%)	0	0	
	HIGH (200-249 MSEC)	1	0	1 (100.0%)	0	
	CONCERN (>=250 MSEC)	1	0	0	1 (100.0%)	
	MISSING	0	0	0	0	
	TOTAL	24	22 (91.7%)	1 (4.2%)	1 (4.2%)	

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 33/WEEK 120

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<200 MSEC)	83	78	(94.0%)	5	(6.0%)	0
	HIGH (200-249 MSEC)	3	2	(66.7%)	1	(33.3%)	0
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	0	0		0		0
	TOTAL	87	80	(92.0%)	6	(6.9%)	1 (1.1%)
SB 207499	NORMAL (<200 MSEC)	165	160	(97.0%)	5	(3.0%)	0
	HIGH (200-249 MSEC)	14	3	(21.4%)	9	(64.3%)	2 (14.3%)
	CONCERN (>=250 MSEC)	0	0		0		0
	MISSING	0	0		0		0
	TOTAL	179	163	(91.1%)	14	(7.8%)	2 (1.1%)
TOTAL	NORMAL (<200 MSEC)	248	238	(96.0%)	10	(4.0%)	0
	HIGH (200-249 MSEC)	17	5	(29.4%)	10	(58.8%)	2 (11.8%)
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	0	0		0		0
	TOTAL	266	243	(91.4%)	20	(7.5%)	3 (1.1%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 34/WEEK 124

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----		
			NORMAL	HIGH	CONCERN
PLACEBO	NORMAL (<200 MSEC)	3	3 (100.0%)	0	0
	HIGH (200-249 MSEC)	0	0	0	0
	CONCERN (>=250 MSEC)	0	0	0	0
	MISSING	0	0	0	0
	TOTAL	3	3 (100.0%)	0	0
SB 207499	NORMAL (<200 MSEC)	3	3 (100.0%)	0	0
	HIGH (200-249 MSEC)	0	0	0	0
	CONCERN (>=250 MSEC)	0	0	0	0
	MISSING	0	0	0	0
	TOTAL	3	3 (100.0%)	0	0
TOTAL	NORMAL (<200 MSEC)	6	6 (100.0%)	0	0
	HIGH (200-249 MSEC)	0	0	0	0
	CONCERN (>=250 MSEC)	0	0	0	0
	MISSING	0	0	0	0
	TOTAL	6	6 (100.0%)	0	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 35/WEEK 128

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL	HIGH	CONCERN	
PLACEBO	NORMAL (<200 MSEC)	3	3 (100.0%)	0	0	
	HIGH (200-249 MSEC)	0	0	0	0	
	CONCERN (>=250 MSEC)	0	0	0	0	
	MISSING	0	0	0	0	
	TOTAL	3	3 (100.0%)	0	0	
SB 207499	NORMAL (<200 MSEC)	3	3 (100.0%)	0	0	
	HIGH (200-249 MSEC)	0	0	0	0	
	CONCERN (>=250 MSEC)	0	0	0	0	
	MISSING	0	0	0	0	
	TOTAL	3	3 (100.0%)	0	0	
TOTAL	NORMAL (<200 MSEC)	6	6 (100.0%)	0	0	
	HIGH (200-249 MSEC)	0	0	0	0	
	CONCERN (>=250 MSEC)	0	0	0	0	
	MISSING	0	0	0	0	
	TOTAL	6	6 (100.0%)	0	0	

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 36/WEEK 132

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		HIGH	CONCERN
PLACEBO	NORMAL (<200 MSEC)	33	33	(100.0%)	0	0
	HIGH (200-249 MSEC)	2	2	(100.0%)	0	0
	CONCERN (>=250 MSEC)	0	0		0	0
	MISSING	0	0		0	0
	TOTAL	35	35	(100.0%)	0	0
SB 207499	NORMAL (<200 MSEC)	52	50	(96.2%)	2 (3.8%)	0
	HIGH (200-249 MSEC)	3	1	(33.3%)	1 (33.3%)	1 (33.3%)
	CONCERN (>=250 MSEC)	0	0		0	0
	MISSING	0	0		0	0
	TOTAL	55	51	(92.7%)	3 (5.5%)	1 (1.8%)
TOTAL	NORMAL (<200 MSEC)	85	83	(97.6%)	2 (2.4%)	0
	HIGH (200-249 MSEC)	5	3	(60.0%)	1 (20.0%)	1 (20.0%)
	CONCERN (>=250 MSEC)	0	0		0	0
	MISSING	0	0		0	0
	TOTAL	90	86	(95.6%)	3 (3.3%)	1 (1.1%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: VISIT 37/WEEK 136

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----		
			NORMAL	HIGH	CONCERN
PLACEBO	NORMAL (<200 MSEC)	0	0	0	0
	HIGH (200-249 MSEC)	0	0	0	0
	CONCERN (>=250 MSEC)	0	0	0	0
	MISSING	0	0	0	0
	TOTAL	0	0	0	0
SB 207499	NORMAL (<200 MSEC)	2	2 (100.0%)	0	0
	HIGH (200-249 MSEC)	0	0	0	0
	CONCERN (>=250 MSEC)	0	0	0	0
	MISSING	0	0	0	0
	TOTAL	2	2 (100.0%)	0	0
TOTAL	NORMAL (<200 MSEC)	2	2 (100.0%)	0	0
	HIGH (200-249 MSEC)	0	0	0	0
	CONCERN (>=250 MSEC)	0	0	0	0
	MISSING	0	0	0	0
	TOTAL	2	2 (100.0%)	0	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: TOTAL ON-THERAPY

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<200 MSEC)	220	203	(92.3%)	17	(7.7%)	0
	HIGH (200-249 MSEC)	11	1	(9.1%)	10	(90.9%)	0
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	2	1	(50.0%)	1	(50.0%)	0
	TOTAL	234	205	(87.6%)	28	(12.0%)	1 (0.4%)
SB 207499	NORMAL (<200 MSEC)	434	379	(87.3%)	54	(12.4%)	1 (0.2%)
	HIGH (200-249 MSEC)	26	2	(7.7%)	16	(61.5%)	8 (30.8%)
	CONCERN (>=250 MSEC)	2	0		0		2 (100.0%)
	MISSING	3	2	(66.7%)	0		1 (33.3%)
	TOTAL	465	383	(82.4%)	70	(15.1%)	12 (2.6%)
TOTAL	NORMAL (<200 MSEC)	654	582	(89.0%)	71	(10.9%)	1 (0.2%)
	HIGH (200-249 MSEC)	37	3	(8.1%)	26	(70.3%)	8 (21.6%)
	CONCERN (>=250 MSEC)	3	0		0		3 (100.0%)
	MISSING	5	3	(60.0%)	1	(20.0%)	1 (20.0%)
	TOTAL	699	588	(84.1%)	98	(14.0%)	13 (1.9%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: PR TIME POINT: ENDPOINT

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<200 MSEC)	220	215	(97.7%)	5	(2.3%)	0
	HIGH (200-249 MSEC)	11	4	(36.4%)	7	(63.6%)	0
	CONCERN (>=250 MSEC)	1	0		0		1 (100.0%)
	MISSING	2	1	(50.0%)	1	(50.0%)	0
	TOTAL	234	220	(94.0%)	13	(5.6%)	1 (0.4%)
SB 207499	NORMAL (<200 MSEC)	434	423	(97.5%)	11	(2.5%)	0
	HIGH (200-249 MSEC)	26	8	(30.8%)	14	(53.8%)	4 (15.4%)
	CONCERN (>=250 MSEC)	2	0		0		2 (100.0%)
	MISSING	3	2	(66.7%)	0		1 (33.3%)
	TOTAL	465	433	(93.1%)	25	(5.4%)	7 (1.5%)
TOTAL	NORMAL (<200 MSEC)	654	638	(97.6%)	16	(2.4%)	0
	HIGH (200-249 MSEC)	37	12	(32.4%)	21	(56.8%)	4 (10.8%)
	CONCERN (>=250 MSEC)	3	0		0		3 (100.0%)
	MISSING	5	3	(60.0%)	1	(20.0%)	1 (20.0%)
	TOTAL	699	653	(93.4%)	38	(5.4%)	8 (1.1%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 2/WEEK 1

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN

PLACEBO	NORMAL (<120 MSEC)	217	207	(95.4%)	10	(4.6%)	0
	HIGH (120-199 MSEC)	17	3	(17.6%)	14	(82.4%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	234	210	(89.7%)	24	(10.3%)	0
SB 207499	NORMAL (<120 MSEC)	435	428	(98.4%)	7	(1.6%)	0
	HIGH (120-199 MSEC)	27	4	(14.8%)	23	(85.2%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	462	432	(93.5%)	30	(6.5%)	0
TOTAL	NORMAL (<120 MSEC)	652	635	(97.4%)	17	(2.6%)	0
	HIGH (120-199 MSEC)	44	7	(15.9%)	37	(84.1%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	696	642	(92.2%)	54	(7.8%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 3/WEEK 2

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<120 MSEC)	209	202	(96.7%)	7	(3.3%)	0
	HIGH (120-199 MSEC)	14	4	(28.6%)	10	(71.4%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	223	206	(92.4%)	17	(7.6%)	0
SB 207499	NORMAL (<120 MSEC)	424	414	(97.6%)	10	(2.4%)	0
	HIGH (120-199 MSEC)	28	2	(7.1%)	26	(92.9%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	452	416	(92.0%)	36	(8.0%)	0
TOTAL	NORMAL (<120 MSEC)	633	616	(97.3%)	17	(2.7%)	0
	HIGH (120-199 MSEC)	42	6	(14.3%)	36	(85.7%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	675	622	(92.1%)	53	(7.9%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 4/WEEK 4

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN

PLACEBO	NORMAL (<120 MSEC)	200	193	(96.5%)	7	(3.5%)	0
	HIGH (120-199 MSEC)	15	3	(20.0%)	12	(80.0%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	215	196	(91.2%)	19	(8.8%)	0
SB 207499	NORMAL (<120 MSEC)	431	422	(97.9%)	9	(2.1%)	0
	HIGH (120-199 MSEC)	27	3	(11.1%)	24	(88.9%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	458	425	(92.8%)	33	(7.2%)	0
TOTAL	NORMAL (<120 MSEC)	631	615	(97.5%)	16	(2.5%)	0
	HIGH (120-199 MSEC)	42	6	(14.3%)	36	(85.7%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	673	621	(92.3%)	52	(7.7%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 5/WEEK 8

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN

PLACEBO	NORMAL (<120 MSEC)	199	194	(97.5%)	5	(2.5%)	0
	HIGH (120-199 MSEC)	14	2	(14.3%)	12	(85.7%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	213	196	(92.0%)	17	(8.0%)	0
SB 207499	NORMAL (<120 MSEC)	420	416	(99.0%)	4	(1.0%)	0
	HIGH (120-199 MSEC)	27	4	(14.8%)	23	(85.2%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	447	420	(94.0%)	27	(6.0%)	0
TOTAL	NORMAL (<120 MSEC)	619	610	(98.5%)	9	(1.5%)	0
	HIGH (120-199 MSEC)	41	6	(14.6%)	35	(85.4%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	660	616	(93.3%)	44	(6.7%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 6/WEEK 12

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN

PLACEBO	NORMAL (<120 MSEC)	195	189	(96.9%)	6	(3.1%)	0
	HIGH (120-199 MSEC)	13	2	(15.4%)	11	(84.6%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	208	191	(91.8%)	17	(8.2%)	0
SB 207499	NORMAL (<120 MSEC)	417	410	(98.3%)	7	(1.7%)	0
	HIGH (120-199 MSEC)	27	3	(11.1%)	24	(88.9%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	444	413	(93.0%)	31	(7.0%)	0
TOTAL	NORMAL (<120 MSEC)	612	599	(97.9%)	13	(2.1%)	0
	HIGH (120-199 MSEC)	40	5	(12.5%)	35	(87.5%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	652	604	(92.6%)	48	(7.4%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 7/WEEK 16

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN

PLACEBO	NORMAL (<120 MSEC)	189	179	(94.7%)	10	(5.3%)	0
	HIGH (120-199 MSEC)	13	1	(7.7%)	12	(92.3%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	202	180	(89.1%)	22	(10.9%)	0
SB 207499	NORMAL (<120 MSEC)	410	405	(98.8%)	5	(1.2%)	0
	HIGH (120-199 MSEC)	26	2	(7.7%)	24	(92.3%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	436	407	(93.3%)	29	(6.7%)	0
TOTAL	NORMAL (<120 MSEC)	599	584	(97.5%)	15	(2.5%)	0
	HIGH (120-199 MSEC)	39	3	(7.7%)	36	(92.3%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	638	587	(92.0%)	51	(8.0%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 8/WEEK 20

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN

PLACEBO	NORMAL (<120 MSEC)	185	180	(97.3%)	5	(2.7%)	0
	HIGH (120-199 MSEC)	12	1	(8.3%)	11	(91.7%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	197	181	(91.9%)	16	(8.1%)	0
SB 207499	NORMAL (<120 MSEC)	406	400	(98.5%)	6	(1.5%)	0
	HIGH (120-199 MSEC)	26	2	(7.7%)	24	(92.3%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	432	402	(93.1%)	30	(6.9%)	0
TOTAL	NORMAL (<120 MSEC)	591	580	(98.1%)	11	(1.9%)	0
	HIGH (120-199 MSEC)	38	3	(7.9%)	35	(92.1%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	629	583	(92.7%)	46	(7.3%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 9/WEEK 24

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN

PLACEBO	NORMAL (<120 MSEC)	181	177	(97.8%)	4	(2.2%)	0
	HIGH (120-199 MSEC)	12	2	(16.7%)	10	(83.3%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	193	179	(92.7%)	14	(7.3%)	0
SB 207499	NORMAL (<120 MSEC)	403	393	(97.5%)	10	(2.5%)	0
	HIGH (120-199 MSEC)	24	1	(4.2%)	23	(95.8%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	427	394	(92.3%)	33	(7.7%)	0
TOTAL	NORMAL (<120 MSEC)	584	570	(97.6%)	14	(2.4%)	0
	HIGH (120-199 MSEC)	36	3	(8.3%)	33	(91.7%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	620	573	(92.4%)	47	(7.6%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 10/WEEK 28

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN

PLACEBO	NORMAL (<120 MSEC)	177	173	(97.7%)	4	(2.3%)	0
	HIGH (120-199 MSEC)	12	2	(16.7%)	10	(83.3%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	189	175	(92.6%)	14	(7.4%)	0
SB 207499	NORMAL (<120 MSEC)	397	389	(98.0%)	8	(2.0%)	0
	HIGH (120-199 MSEC)	25	2	(8.0%)	23	(92.0%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	422	391	(92.7%)	31	(7.3%)	0
TOTAL	NORMAL (<120 MSEC)	574	562	(97.9%)	12	(2.1%)	0
	HIGH (120-199 MSEC)	37	4	(10.8%)	33	(89.2%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	611	566	(92.6%)	45	(7.4%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 11/WEEK 32

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN

PLACEBO	NORMAL (<120 MSEC)	175	171	(97.7%)	4	(2.3%)	0
	HIGH (120-199 MSEC)	11	2	(18.2%)	9	(81.8%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	186	173	(93.0%)	13	(7.0%)	0
SB 207499	NORMAL (<120 MSEC)	395	389	(98.5%)	6	(1.5%)	0
	HIGH (120-199 MSEC)	24	3	(12.5%)	21	(87.5%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	419	392	(93.6%)	27	(6.4%)	0
TOTAL	NORMAL (<120 MSEC)	570	560	(98.2%)	10	(1.8%)	0
	HIGH (120-199 MSEC)	35	5	(14.3%)	30	(85.7%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	605	565	(93.4%)	40	(6.6%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 12/WEEK 36

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN

PLACEBO	NORMAL (<120 MSEC)	176	172	(97.7%)	4	(2.3%)	0
	HIGH (120-199 MSEC)	11	1	(9.1%)	10	(90.9%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	187	173	(92.5%)	14	(7.5%)	0
SB 207499	NORMAL (<120 MSEC)	386	382	(99.0%)	4	(1.0%)	0
	HIGH (120-199 MSEC)	24	2	(8.3%)	22	(91.7%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	410	384	(93.7%)	26	(6.3%)	0
TOTAL	NORMAL (<120 MSEC)	562	554	(98.6%)	8	(1.4%)	0
	HIGH (120-199 MSEC)	35	3	(8.6%)	32	(91.4%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	597	557	(93.3%)	40	(6.7%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 13/WEEK 40

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN

PLACEBO	NORMAL (<120 MSEC)	174	172	(98.9%)	2	(1.1%)	0
	HIGH (120-199 MSEC)	11	2	(18.2%)	9	(81.8%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	185	174	(94.1%)	11	(5.9%)	0
SB 207499	NORMAL (<120 MSEC)	381	375	(98.4%)	6	(1.6%)	0
	HIGH (120-199 MSEC)	24	2	(8.3%)	22	(91.7%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	405	377	(93.1%)	28	(6.9%)	0
TOTAL	NORMAL (<120 MSEC)	555	547	(98.6%)	8	(1.4%)	0
	HIGH (120-199 MSEC)	35	4	(11.4%)	31	(88.6%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	590	551	(93.4%)	39	(6.6%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 14/WEEK 44

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN

PLACEBO	NORMAL (<120 MSEC)	172	169	(98.3%)	3	(1.7%)	0
	HIGH (120-199 MSEC)	11	2	(18.2%)	9	(81.8%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	183	171	(93.4%)	12	(6.6%)	0
SB 207499	NORMAL (<120 MSEC)	380	374	(98.4%)	6	(1.6%)	0
	HIGH (120-199 MSEC)	24	2	(8.3%)	22	(91.7%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	404	376	(93.1%)	28	(6.9%)	0
TOTAL	NORMAL (<120 MSEC)	552	543	(98.4%)	9	(1.6%)	0
	HIGH (120-199 MSEC)	35	4	(11.4%)	31	(88.6%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	587	547	(93.2%)	40	(6.8%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 15/WEEK 48

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN

PLACEBO	NORMAL (<120 MSEC)	173	168	(97.1%)	5	(2.9%)	0
	HIGH (120-199 MSEC)	11	2	(18.2%)	9	(81.8%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	184	170	(92.4%)	14	(7.6%)	0
SB 207499	NORMAL (<120 MSEC)	373	366	(98.1%)	7	(1.9%)	0
	HIGH (120-199 MSEC)	24	2	(8.3%)	22	(91.7%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	397	368	(92.7%)	29	(7.3%)	0
TOTAL	NORMAL (<120 MSEC)	546	534	(97.8%)	12	(2.2%)	0
	HIGH (120-199 MSEC)	35	4	(11.4%)	31	(88.6%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	581	538	(92.6%)	43	(7.4%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 16/WEEK 52

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<120 MSEC)	169	164	(97.0%)	5	(3.0%)	0
	HIGH (120-199 MSEC)	11	1	(9.1%)	10	(90.9%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	180	165	(91.7%)	15	(8.3%)	0
SB 207499	NORMAL (<120 MSEC)	363	356	(98.1%)	7	(1.9%)	0
	HIGH (120-199 MSEC)	21	3	(14.3%)	18	(85.7%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	384	359	(93.5%)	25	(6.5%)	0
TOTAL	NORMAL (<120 MSEC)	532	520	(97.7%)	12	(2.3%)	0
	HIGH (120-199 MSEC)	32	4	(12.5%)	28	(87.5%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	564	524	(92.9%)	40	(7.1%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 17/WEEK 56

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<120 MSEC)	158	155	(98.1%)	3	(1.9%)	0
	HIGH (120-199 MSEC)	11	1	(9.1%)	10	(90.9%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	169	156	(92.3%)	13	(7.7%)	0
SB 207499	NORMAL (<120 MSEC)	344	335	(97.4%)	9	(2.6%)	0
	HIGH (120-199 MSEC)	20	1	(5.0%)	19	(95.0%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	364	336	(92.3%)	28	(7.7%)	0
TOTAL	NORMAL (<120 MSEC)	502	490	(97.6%)	12	(2.4%)	0
	HIGH (120-199 MSEC)	31	2	(6.5%)	29	(93.5%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	533	492	(92.3%)	41	(7.7%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 18/WEEK 60

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN

PLACEBO	NORMAL (<120 MSEC)	162	159	(98.1%)	3	(1.9%)	0
	HIGH (120-199 MSEC)	11	1	(9.1%)	10	(90.9%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	173	160	(92.5%)	13	(7.5%)	0
SB 207499	NORMAL (<120 MSEC)	351	342	(97.4%)	9	(2.6%)	0
	HIGH (120-199 MSEC)	23	2	(8.7%)	21	(91.3%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	374	344	(92.0%)	30	(8.0%)	0
TOTAL	NORMAL (<120 MSEC)	513	501	(97.7%)	12	(2.3%)	0
	HIGH (120-199 MSEC)	34	3	(8.8%)	31	(91.2%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	547	504	(92.1%)	43	(7.9%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 19/WEEK 64

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN

PLACEBO	NORMAL (<120 MSEC)	134	132	(98.5%)	2	(1.5%)	0
	HIGH (120-199 MSEC)	8	1	(12.5%)	7	(87.5%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	142	133	(93.7%)	9	(6.3%)	0
SB 207499	NORMAL (<120 MSEC)	293	286	(97.6%)	7	(2.4%)	0
	HIGH (120-199 MSEC)	15	0		15	(100.0%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	308	286	(92.9%)	22	(7.1%)	0
TOTAL	NORMAL (<120 MSEC)	427	418	(97.9%)	9	(2.1%)	0
	HIGH (120-199 MSEC)	23	1	(4.3%)	22	(95.7%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	450	419	(93.1%)	31	(6.9%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 20/WEEK 68

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN

PLACEBO	NORMAL (<120 MSEC)	132	127	(96.2%)	5	(3.8%)	0
	HIGH (120-199 MSEC)	8	1	(12.5%)	7	(87.5%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	140	128	(91.4%)	12	(8.6%)	0
SB 207499	NORMAL (<120 MSEC)	280	272	(97.1%)	8	(2.9%)	0
	HIGH (120-199 MSEC)	15	1	(6.7%)	14	(93.3%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	295	273	(92.5%)	22	(7.5%)	0
TOTAL	NORMAL (<120 MSEC)	412	399	(96.8%)	13	(3.2%)	0
	HIGH (120-199 MSEC)	23	2	(8.7%)	21	(91.3%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	435	401	(92.2%)	34	(7.8%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 21/WEEK 72

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN

PLACEBO	NORMAL (<120 MSEC)	160	155	(96.9%)	5	(3.1%)	0
	HIGH (120-199 MSEC)	10	3	(30.0%)	7	(70.0%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	170	158	(92.9%)	12	(7.1%)	0
SB 207499	NORMAL (<120 MSEC)	335	328	(97.9%)	7	(2.1%)	0
	HIGH (120-199 MSEC)	22	2	(9.1%)	20	(90.9%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	357	330	(92.4%)	27	(7.6%)	0
TOTAL	NORMAL (<120 MSEC)	495	483	(97.6%)	12	(2.4%)	0
	HIGH (120-199 MSEC)	32	5	(15.6%)	27	(84.4%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	527	488	(92.6%)	39	(7.4%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 22/WEEK 76

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN

PLACEBO	NORMAL (<120 MSEC)	96	93	(96.9%)	3	(3.1%)	0
	HIGH (120-199 MSEC)	4	1	(25.0%)	3	(75.0%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	100	94	(94.0%)	6	(6.0%)	0
SB 207499	NORMAL (<120 MSEC)	191	188	(98.4%)	3	(1.6%)	0
	HIGH (120-199 MSEC)	7	0		7	(100.0%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	198	188	(94.9%)	10	(5.1%)	0
TOTAL	NORMAL (<120 MSEC)	287	281	(97.9%)	6	(2.1%)	0
	HIGH (120-199 MSEC)	11	1	(9.1%)	10	(90.9%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	298	282	(94.6%)	16	(5.4%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 23/WEEK 80

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN

PLACEBO	NORMAL (<120 MSEC)	94	93	(98.9%)	1	(1.1%)	0
	HIGH (120-199 MSEC)	4	1	(25.0%)	3	(75.0%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	98	94	(95.9%)	4	(4.1%)	0
SB 207499	NORMAL (<120 MSEC)	187	182	(97.3%)	5	(2.7%)	0
	HIGH (120-199 MSEC)	6	0		6	(100.0%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	193	182	(94.3%)	11	(5.7%)	0
TOTAL	NORMAL (<120 MSEC)	281	275	(97.9%)	6	(2.1%)	0
	HIGH (120-199 MSEC)	10	1	(10.0%)	9	(90.0%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	291	276	(94.8%)	15	(5.2%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 24/WEEK 84

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN

PLACEBO	NORMAL (<120 MSEC)	154	152	(98.7%)	2	(1.3%)	0
	HIGH (120-199 MSEC)	9	2	(22.2%)	7	(77.8%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	163	154	(94.5%)	9	(5.5%)	0
SB 207499	NORMAL (<120 MSEC)	314	305	(97.1%)	9	(2.9%)	0
	HIGH (120-199 MSEC)	20	1	(5.0%)	19	(95.0%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	334	306	(91.6%)	28	(8.4%)	0
TOTAL	NORMAL (<120 MSEC)	468	457	(97.6%)	11	(2.4%)	0
	HIGH (120-199 MSEC)	29	3	(10.3%)	26	(89.7%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	497	460	(92.6%)	37	(7.4%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 25/WEEK 88

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<120 MSEC)	51	51	(100.0%)	0		0
	HIGH (120-199 MSEC)	2	0		2	(100.0%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	53	51	(96.2%)	2	(3.8%)	0
SB 207499	NORMAL (<120 MSEC)	94	91	(96.8%)	3	(3.2%)	0
	HIGH (120-199 MSEC)	3	0		3	(100.0%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	97	91	(93.8%)	6	(6.2%)	0
TOTAL	NORMAL (<120 MSEC)	145	142	(97.9%)	3	(2.1%)	0
	HIGH (120-199 MSEC)	5	0		5	(100.0%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	150	142	(94.7%)	8	(5.3%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 26/WEEK 92

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN

PLACEBO	NORMAL (<120 MSEC)	50	47	(94.0%)	3	(6.0%)	0
	HIGH (120-199 MSEC)	2	0		2	(100.0%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	52	47	(90.4%)	5	(9.6%)	0
SB 207499	NORMAL (<120 MSEC)	93	89	(95.7%)	4	(4.3%)	0
	HIGH (120-199 MSEC)	3	0		3	(100.0%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	96	89	(92.7%)	7	(7.3%)	0
TOTAL	NORMAL (<120 MSEC)	143	136	(95.1%)	7	(4.9%)	0
	HIGH (120-199 MSEC)	5	0		5	(100.0%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	148	136	(91.9%)	12	(8.1%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 27/WEEK 96

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL (<120 MSEC)	150	144	(96.0%)	6	(4.0%)	0
	HIGH (120-199 MSEC)	10	1	(10.0%)	9	(90.0%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	160	145	(90.6%)	15	(9.4%)	0
SB 207499	NORMAL (<120 MSEC)	307	297	(96.7%)	10	(3.3%)	0
	HIGH (120-199 MSEC)	21	1	(4.8%)	20	(95.2%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	328	298	(90.9%)	30	(9.1%)	0
TOTAL	NORMAL (<120 MSEC)	457	441	(96.5%)	16	(3.5%)	0
	HIGH (120-199 MSEC)	31	2	(6.5%)	29	(93.5%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	488	443	(90.8%)	45	(9.2%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 28/WEEK 100

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		HIGH	CONCERN
PLACEBO	NORMAL (<120 MSEC)	22	22	(100.0%)	0	0
	HIGH (120-199 MSEC)	0	0		0	0
	CONCERN (>=200 MSEC)	0	0		0	0
	TOTAL	22	22	(100.0%)	0	0
SB 207499	NORMAL (<120 MSEC)	47	45	(95.7%)	2 (4.3%)	0
	HIGH (120-199 MSEC)	2	0		2 (100.0%)	0
	CONCERN (>=200 MSEC)	0	0		0	0
	TOTAL	49	45	(91.8%)	4 (8.2%)	0
TOTAL	NORMAL (<120 MSEC)	69	67	(97.1%)	2 (2.9%)	0
	HIGH (120-199 MSEC)	2	0		2 (100.0%)	0
	CONCERN (>=200 MSEC)	0	0		0	0
	TOTAL	71	67	(94.4%)	4 (5.6%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 29/WEEK 104

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN

PLACEBO	NORMAL (<120 MSEC)	18	17	(94.4%)	1	(5.6%)	0
	HIGH (120-199 MSEC)	0	0		0		0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	18	17	(94.4%)	1	(5.6%)	0
SB 207499	NORMAL (<120 MSEC)	39	37	(94.9%)	2	(5.1%)	0
	HIGH (120-199 MSEC)	1	0		1	(100.0%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	40	37	(92.5%)	3	(7.5%)	0
TOTAL	NORMAL (<120 MSEC)	57	54	(94.7%)	3	(5.3%)	0
	HIGH (120-199 MSEC)	1	0		1	(100.0%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	58	54	(93.1%)	4	(6.9%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 30/WEEK 108

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN

PLACEBO	NORMAL (<120 MSEC)	118	109	(92.4%)	9	(7.6%)	0
	HIGH (120-199 MSEC)	8	2	(25.0%)	6	(75.0%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	126	111	(88.1%)	15	(11.9%)	0
SB 207499	NORMAL (<120 MSEC)	253	245	(96.8%)	8	(3.2%)	0
	HIGH (120-199 MSEC)	19	3	(15.8%)	16	(84.2%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	272	248	(91.2%)	24	(8.8%)	0
TOTAL	NORMAL (<120 MSEC)	371	354	(95.4%)	17	(4.6%)	0
	HIGH (120-199 MSEC)	27	5	(18.5%)	22	(81.5%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	398	359	(90.2%)	39	(9.8%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 31/WEEK 112

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		HIGH	CONCERN
PLACEBO	NORMAL (<120 MSEC)	9	9	(100.0%)	0	0
	HIGH (120-199 MSEC)	0	0		0	0
	CONCERN (>=200 MSEC)	0	0		0	0
	TOTAL	9	9	(100.0%)	0	0
SB 207499	NORMAL (<120 MSEC)	17	17	(100.0%)	0	0
	HIGH (120-199 MSEC)	1	0		1 (100.0%)	0
	CONCERN (>=200 MSEC)	0	0		0	0
	TOTAL	18	17	(94.4%)	1 (5.6%)	0
TOTAL	NORMAL (<120 MSEC)	26	26	(100.0%)	0	0
	HIGH (120-199 MSEC)	1	0		1 (100.0%)	0
	CONCERN (>=200 MSEC)	0	0		0	0
	TOTAL	27	26	(96.3%)	1 (3.7%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 32/WEEK 116

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL	HIGH	CONCERN	
PLACEBO	NORMAL (<120 MSEC)	9	8 (88.9%)	1 (11.1%)	0	
	HIGH (120-199 MSEC)	0	0	0	0	
	CONCERN (>=200 MSEC)	0	0	0	0	
	TOTAL	9	8 (88.9%)	1 (11.1%)	0	
SB 207499	NORMAL (<120 MSEC)	15	15 (100.0%)	0	0	
	HIGH (120-199 MSEC)	1	0	1 (100.0%)	0	
	CONCERN (>=200 MSEC)	0	0	0	0	
	TOTAL	16	15 (93.8%)	1 (6.3%)	0	
TOTAL	NORMAL (<120 MSEC)	24	23 (95.8%)	1 (4.2%)	0	
	HIGH (120-199 MSEC)	1	0	1 (100.0%)	0	
	CONCERN (>=200 MSEC)	0	0	0	0	
	TOTAL	25	23 (92.0%)	2 (8.0%)	0	

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 33/WEEK 120

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN

PLACEBO	NORMAL (<120 MSEC)	85	81	(95.3%)	4	(4.7%)	0
	HIGH (120-199 MSEC)	6	1	(16.7%)	5	(83.3%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	91	82	(90.1%)	9	(9.9%)	0
SB 207499	NORMAL (<120 MSEC)	178	174	(97.8%)	4	(2.2%)	0
	HIGH (120-199 MSEC)	9	0		9	(100.0%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	187	174	(93.0%)	13	(7.0%)	0
TOTAL	NORMAL (<120 MSEC)	263	255	(97.0%)	8	(3.0%)	0
	HIGH (120-199 MSEC)	15	1	(6.7%)	14	(93.3%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	278	256	(92.1%)	22	(7.9%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 34/WEEK 124

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		HIGH	CONCERN
PLACEBO	NORMAL (<120 MSEC)	3	3	(100.0%)	0	0
	HIGH (120-199 MSEC)	0	0		0	0
	CONCERN (>=200 MSEC)	0	0		0	0
	TOTAL	3	3	(100.0%)	0	0
SB 207499	NORMAL (<120 MSEC)	3	2	(66.7%)	1	(33.3%)
	HIGH (120-199 MSEC)	0	0		0	0
	CONCERN (>=200 MSEC)	0	0		0	0
	TOTAL	3	2	(66.7%)	1	(33.3%)
TOTAL	NORMAL (<120 MSEC)	6	5	(83.3%)	1	(16.7%)
	HIGH (120-199 MSEC)	0	0		0	0
	CONCERN (>=200 MSEC)	0	0		0	0
	TOTAL	6	5	(83.3%)	1	(16.7%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 35/WEEK 128

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL	HIGH	CONCERN	
PLACEBO	NORMAL (<120 MSEC)	3	3	(100.0%)	0	0
	HIGH (120-199 MSEC)	0	0		0	0
	CONCERN (>=200 MSEC)	0	0		0	0
	TOTAL	3	3	(100.0%)	0	0
SB 207499	NORMAL (<120 MSEC)	3	3	(100.0%)	0	0
	HIGH (120-199 MSEC)	0	0		0	0
	CONCERN (>=200 MSEC)	0	0		0	0
	TOTAL	3	3	(100.0%)	0	0
TOTAL	NORMAL (<120 MSEC)	6	6	(100.0%)	0	0
	HIGH (120-199 MSEC)	0	0		0	0
	CONCERN (>=200 MSEC)	0	0		0	0
	TOTAL	6	6	(100.0%)	0	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 36/WEEK 132

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		HIGH	CONCERN
PLACEBO	NORMAL (<120 MSEC)	36	36	(100.0%)	0	0
	HIGH (120-199 MSEC)	0	0		0	0
	CONCERN (>=200 MSEC)	0	0		0	0
	TOTAL	36	36	(100.0%)	0	0
SB 207499	NORMAL (<120 MSEC)	54	54	(100.0%)	0	0
	HIGH (120-199 MSEC)	4	0		4 (100.0%)	0
	CONCERN (>=200 MSEC)	0	0		0	0
	TOTAL	58	54	(93.1%)	4 (6.9%)	0
TOTAL	NORMAL (<120 MSEC)	90	90	(100.0%)	0	0
	HIGH (120-199 MSEC)	4	0		4 (100.0%)	0
	CONCERN (>=200 MSEC)	0	0		0	0
	TOTAL	94	90	(95.7%)	4 (4.3%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: VISIT 37/WEEK 136

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		HIGH	CONCERN
PLACEBO	NORMAL (<120 MSEC)	1	1	(100.0%)	0	0
	HIGH (120-199 MSEC)	0	0		0	0
	CONCERN (>=200 MSEC)	0	0		0	0
	TOTAL	1	1	(100.0%)	0	0
SB 207499	NORMAL (<120 MSEC)	2	2	(100.0%)	0	0
	HIGH (120-199 MSEC)	0	0		0	0
	CONCERN (>=200 MSEC)	0	0		0	0
	TOTAL	2	2	(100.0%)	0	0
TOTAL	NORMAL (<120 MSEC)	3	3	(100.0%)	0	0
	HIGH (120-199 MSEC)	0	0		0	0
	CONCERN (>=200 MSEC)	0	0		0	0
	TOTAL	3	3	(100.0%)	0	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: TOTAL ON-THERAPY

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN

PLACEBO	NORMAL (<120 MSEC)	222	200	(90.1%)	22	(9.9%)	0
	HIGH (120-199 MSEC)	17	1	(5.9%)	16	(94.1%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	239	201	(84.1%)	38	(15.9%)	0
SB 207499	NORMAL (<120 MSEC)	443	403	(91.0%)	40	(9.0%)	0
	HIGH (120-199 MSEC)	28	1	(3.6%)	27	(96.4%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	471	404	(85.8%)	67	(14.2%)	0
TOTAL	NORMAL (<120 MSEC)	665	603	(90.7%)	62	(9.3%)	0
	HIGH (120-199 MSEC)	45	2	(4.4%)	43	(95.6%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	710	605	(85.2%)	105	(14.8%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QRS TIME POINT: ENDPOINT

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN

PLACEBO	NORMAL (<120 MSEC)	222	215	(96.8%)	7	(3.2%)	0
	HIGH (120-199 MSEC)	17	3	(17.6%)	14	(82.4%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	239	218	(91.2%)	21	(8.8%)	0
SB 207499	NORMAL (<120 MSEC)	443	433	(97.7%)	10	(2.3%)	0
	HIGH (120-199 MSEC)	28	4	(14.3%)	24	(85.7%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	471	437	(92.8%)	34	(7.2%)	0
TOTAL	NORMAL (<120 MSEC)	665	648	(97.4%)	17	(2.6%)	0
	HIGH (120-199 MSEC)	45	7	(15.6%)	38	(84.4%)	0
	CONCERN (>=200 MSEC)	0	0		0		0
	TOTAL	710	655	(92.3%)	55	(7.7%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 2/WEEK 1

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (<500 MSEC)	234	234	(100.0%)	0	
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	234	234	(100.0%)	0	
SB 207499	NORMAL (<500 MSEC)	460	459	(99.8%)	1	(0.2%)
	CONCERN (>=500 MSEC)	2	2	(100.0%)	0	
	TOTAL	462	461	(99.8%)	1	(0.2%)
TOTAL	NORMAL (<500 MSEC)	694	693	(99.9%)	1	(0.1%)
	CONCERN (>=500 MSEC)	2	2	(100.0%)	0	
	TOTAL	696	695	(99.9%)	1	(0.1%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 3/WEEK 2

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (<500 MSEC)	223	223	(100.0%)	0	
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	223	223	(100.0%)	0	
SB 207499	NORMAL (<500 MSEC)	450	449	(99.8%)	1	(0.2%)
	CONCERN (>=500 MSEC)	2	2	(100.0%)	0	
	TOTAL	452	451	(99.8%)	1	(0.2%)
TOTAL	NORMAL (<500 MSEC)	673	672	(99.9%)	1	(0.1%)
	CONCERN (>=500 MSEC)	2	2	(100.0%)	0	
	TOTAL	675	674	(99.9%)	1	(0.1%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 4/WEEK 4

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (<500 MSEC)	215	215	(100.0%)	0	
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	215	215	(100.0%)	0	
SB 207499	NORMAL (<500 MSEC)	457	456	(99.8%)	1	(0.2%)
	CONCERN (>=500 MSEC)	1	1	(100.0%)	0	
	TOTAL	458	457	(99.8%)	1	(0.2%)
TOTAL	NORMAL (<500 MSEC)	672	671	(99.9%)	1	(0.1%)
	CONCERN (>=500 MSEC)	1	1	(100.0%)	0	
	TOTAL	673	672	(99.9%)	1	(0.1%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 5/WEEK 8

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----		
			NORMAL		CONCERN

PLACEBO	NORMAL (<500 MSEC)	213	213	(100.0%)	0
	CONCERN (>=500 MSEC)	0	0		0
	TOTAL	213	213	(100.0%)	0
SB 207499	NORMAL (<500 MSEC)	445	445	(100.0%)	0
	CONCERN (>=500 MSEC)	2	2	(100.0%)	0
	TOTAL	447	447	(100.0%)	0
TOTAL	NORMAL (<500 MSEC)	658	658	(100.0%)	0
	CONCERN (>=500 MSEC)	2	2	(100.0%)	0
	TOTAL	660	660	(100.0%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 6/WEEK 12

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (<500 MSEC)	208	208	(100.0%)	0	
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	208	208	(100.0%)	0	
SB 207499	NORMAL (<500 MSEC)	442	440	(99.5%)	2	(0.5%)
	CONCERN (>=500 MSEC)	2	2	(100.0%)	0	
	TOTAL	444	442	(99.5%)	2	(0.5%)
TOTAL	NORMAL (<500 MSEC)	650	648	(99.7%)	2	(0.3%)
	CONCERN (>=500 MSEC)	2	2	(100.0%)	0	
	TOTAL	652	650	(99.7%)	2	(0.3%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 7/WEEK 16

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (<500 MSEC)	202	202	(100.0%)	0	
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	202	202	(100.0%)	0	
SB 207499	NORMAL (<500 MSEC)	435	434	(99.8%)	1	(0.2%)
	CONCERN (>=500 MSEC)	1	1	(100.0%)	0	
	TOTAL	436	435	(99.8%)	1	(0.2%)
TOTAL	NORMAL (<500 MSEC)	637	636	(99.8%)	1	(0.2%)
	CONCERN (>=500 MSEC)	1	1	(100.0%)	0	
	TOTAL	638	637	(99.8%)	1	(0.2%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 8/WEEK 20

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (<500 MSEC)	197	197	(100.0%)	0	
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	197	197	(100.0%)	0	
SB 207499	NORMAL (<500 MSEC)	431	429	(99.5%)	2	(0.5%)
	CONCERN (>=500 MSEC)	1	1	(100.0%)	0	
	TOTAL	432	430	(99.5%)	2	(0.5%)
TOTAL	NORMAL (<500 MSEC)	628	626	(99.7%)	2	(0.3%)
	CONCERN (>=500 MSEC)	1	1	(100.0%)	0	
	TOTAL	629	627	(99.7%)	2	(0.3%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 9/WEEK 24

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (<500 MSEC)	193	193	(100.0%)	0	
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	193	193	(100.0%)	0	
SB 207499	NORMAL (<500 MSEC)	426	424	(99.5%)	2	(0.5%)
	CONCERN (>=500 MSEC)	1	1	(100.0%)	0	
	TOTAL	427	425	(99.5%)	2	(0.5%)
TOTAL	NORMAL (<500 MSEC)	619	617	(99.7%)	2	(0.3%)
	CONCERN (>=500 MSEC)	1	1	(100.0%)	0	
	TOTAL	620	618	(99.7%)	2	(0.3%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 10/WEEK 28

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (<500 MSEC)	190	190	(100.0%)	0	
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	190	190	(100.0%)	0	
SB 207499	NORMAL (<500 MSEC)	421	420	(99.8%)	1	(0.2%)
	CONCERN (>=500 MSEC)	1	1	(100.0%)	0	
	TOTAL	422	421	(99.8%)	1	(0.2%)
TOTAL	NORMAL (<500 MSEC)	611	610	(99.8%)	1	(0.2%)
	CONCERN (>=500 MSEC)	1	1	(100.0%)	0	
	TOTAL	612	611	(99.8%)	1	(0.2%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 11/WEEK 32

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (<500 MSEC)	186	186	(100.0%)	0	
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	186	186	(100.0%)	0	
SB 207499	NORMAL (<500 MSEC)	418	416	(99.5%)	2	(0.5%)
	CONCERN (>=500 MSEC)	1	1	(100.0%)	0	
	TOTAL	419	417	(99.5%)	2	(0.5%)
TOTAL	NORMAL (<500 MSEC)	604	602	(99.7%)	2	(0.3%)
	CONCERN (>=500 MSEC)	1	1	(100.0%)	0	
	TOTAL	605	603	(99.7%)	2	(0.3%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 12/WEEK 36

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (<500 MSEC)	187	187	(100.0%)	0	
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	187	187	(100.0%)	0	
SB 207499	NORMAL (<500 MSEC)	409	407	(99.5%)	2	(0.5%)
	CONCERN (>=500 MSEC)	1	1	(100.0%)	0	
	TOTAL	410	408	(99.5%)	2	(0.5%)
TOTAL	NORMAL (<500 MSEC)	596	594	(99.7%)	2	(0.3%)
	CONCERN (>=500 MSEC)	1	1	(100.0%)	0	
	TOTAL	597	595	(99.7%)	2	(0.3%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 13/WEEK 40

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (<500 MSEC)	185	184	(99.5%)	1	(0.5%)
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	185	184	(99.5%)	1	(0.5%)
SB 207499	NORMAL (<500 MSEC)	404	401	(99.3%)	3	(0.7%)
	CONCERN (>=500 MSEC)	1	1	(100.0%)	0	
	TOTAL	405	402	(99.3%)	3	(0.7%)
TOTAL	NORMAL (<500 MSEC)	589	585	(99.3%)	4	(0.7%)
	CONCERN (>=500 MSEC)	1	1	(100.0%)	0	
	TOTAL	590	586	(99.3%)	4	(0.7%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 14/WEEK 44

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (<500 MSEC)	183	182	(99.5%)	1	(0.5%)
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	183	182	(99.5%)	1	(0.5%)
SB 207499	NORMAL (<500 MSEC)	403	400	(99.3%)	3	(0.7%)
	CONCERN (>=500 MSEC)	1	1	(100.0%)	0	
	TOTAL	404	401	(99.3%)	3	(0.7%)
TOTAL	NORMAL (<500 MSEC)	586	582	(99.3%)	4	(0.7%)
	CONCERN (>=500 MSEC)	1	1	(100.0%)	0	
	TOTAL	587	583	(99.3%)	4	(0.7%)

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2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 15/WEEK 48

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (<500 MSEC)	184	183	(99.5%)	1	(0.5%)
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	184	183	(99.5%)	1	(0.5%)
SB 207499	NORMAL (<500 MSEC)	395	393	(99.5%)	2	(0.5%)
	CONCERN (>=500 MSEC)	1	1	(100.0%)	0	
	TOTAL	396	394	(99.5%)	2	(0.5%)
TOTAL	NORMAL (<500 MSEC)	579	576	(99.5%)	3	(0.5%)
	CONCERN (>=500 MSEC)	1	1	(100.0%)	0	
	TOTAL	580	577	(99.5%)	3	(0.5%)

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3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 16/WEEK 52

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (<500 MSEC)	180	179	(99.4%)	1	(0.6%)
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	180	179	(99.4%)	1	(0.6%)
SB 207499	NORMAL (<500 MSEC)	382	381	(99.7%)	1	(0.3%)
	CONCERN (>=500 MSEC)	1	1	(100.0%)	0	
	TOTAL	383	382	(99.7%)	1	(0.3%)
TOTAL	NORMAL (<500 MSEC)	562	560	(99.6%)	2	(0.4%)
	CONCERN (>=500 MSEC)	1	1	(100.0%)	0	
	TOTAL	563	561	(99.6%)	2	(0.4%)

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3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 17/WEEK 56

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (<500 MSEC)	169	169	(100.0%)	0	
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	169	169	(100.0%)	0	
SB 207499	NORMAL (<500 MSEC)	363	362	(99.7%)	1	(0.3%)
	CONCERN (>=500 MSEC)	1	1	(100.0%)	0	
	TOTAL	364	363	(99.7%)	1	(0.3%)
TOTAL	NORMAL (<500 MSEC)	532	531	(99.8%)	1	(0.2%)
	CONCERN (>=500 MSEC)	1	1	(100.0%)	0	
	TOTAL	533	532	(99.8%)	1	(0.2%)

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2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 18/WEEK 60

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (<500 MSEC)	173	173	(100.0%)	0	
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	173	173	(100.0%)	0	
SB 207499	NORMAL (<500 MSEC)	372	369	(99.2%)	3	(0.8%)
	CONCERN (>=500 MSEC)	1	1	(100.0%)	0	
	TOTAL	373	370	(99.2%)	3	(0.8%)
TOTAL	NORMAL (<500 MSEC)	545	542	(99.4%)	3	(0.6%)
	CONCERN (>=500 MSEC)	1	1	(100.0%)	0	
	TOTAL	546	543	(99.5%)	3	(0.5%)

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2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 19/WEEK 64

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (<500 MSEC)	142	142	(100.0%)	0	
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	142	142	(100.0%)	0	
SB 207499	NORMAL (<500 MSEC)	308	307	(99.7%)	1	(0.3%)
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	308	307	(99.7%)	1	(0.3%)
TOTAL	NORMAL (<500 MSEC)	450	449	(99.8%)	1	(0.2%)
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	450	449	(99.8%)	1	(0.2%)

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3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 20/WEEK 68

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (<500 MSEC)	140	139	(99.3%)	1	(0.7%)
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	140	139	(99.3%)	1	(0.7%)
SB 207499	NORMAL (<500 MSEC)	295	294	(99.7%)	1	(0.3%)
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	295	294	(99.7%)	1	(0.3%)
TOTAL	NORMAL (<500 MSEC)	435	433	(99.5%)	2	(0.5%)
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	435	433	(99.5%)	2	(0.5%)

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3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 21/WEEK 72

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (<500 MSEC)	170	169	(99.4%)	1	(0.6%)
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	170	169	(99.4%)	1	(0.6%)
SB 207499	NORMAL (<500 MSEC)	356	352	(98.9%)	4	(1.1%)
	CONCERN (>=500 MSEC)	1	1	(100.0%)	0	
	TOTAL	357	353	(98.9%)	4	(1.1%)
TOTAL	NORMAL (<500 MSEC)	526	521	(99.0%)	5	(1.0%)
	CONCERN (>=500 MSEC)	1	1	(100.0%)	0	
	TOTAL	527	522	(99.1%)	5	(0.9%)

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2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 22/WEEK 76

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----		
			NORMAL		CONCERN

PLACEBO	NORMAL (<500 MSEC)	100	100	(100.0%)	0
	CONCERN (>=500 MSEC)	0	0		0
	TOTAL	100	100	(100.0%)	0
SB 207499	NORMAL (<500 MSEC)	198	198	(100.0%)	0
	CONCERN (>=500 MSEC)	0	0		0
	TOTAL	198	198	(100.0%)	0
TOTAL	NORMAL (<500 MSEC)	298	298	(100.0%)	0
	CONCERN (>=500 MSEC)	0	0		0
	TOTAL	298	298	(100.0%)	0

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3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 23/WEEK 80

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (<500 MSEC)	98	98	(100.0%)	0	
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	98	98	(100.0%)	0	
SB 207499	NORMAL (<500 MSEC)	193	192	(99.5%)	1	(0.5%)
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	193	192	(99.5%)	1	(0.5%)
TOTAL	NORMAL (<500 MSEC)	291	290	(99.7%)	1	(0.3%)
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	291	290	(99.7%)	1	(0.3%)

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3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 24/WEEK 84

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (<500 MSEC)	163	162	(99.4%)	1	(0.6%)
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	163	162	(99.4%)	1	(0.6%)
SB 207499	NORMAL (<500 MSEC)	333	331	(99.4%)	2	(0.6%)
	CONCERN (>=500 MSEC)	1	1	(100.0%)	0	
	TOTAL	334	332	(99.4%)	2	(0.6%)
TOTAL	NORMAL (<500 MSEC)	496	493	(99.4%)	3	(0.6%)
	CONCERN (>=500 MSEC)	1	1	(100.0%)	0	
	TOTAL	497	494	(99.4%)	3	(0.6%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
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3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 25/WEEK 88

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----		
			NORMAL		CONCERN
PLACEBO	NORMAL (<500 MSEC)	53	53	(100.0%)	0
	CONCERN (>=500 MSEC)	0	0		0
	TOTAL	53	53	(100.0%)	0
SB 207499	NORMAL (<500 MSEC)	97	97	(100.0%)	0
	CONCERN (>=500 MSEC)	0	0		0
	TOTAL	97	97	(100.0%)	0
TOTAL	NORMAL (<500 MSEC)	150	150	(100.0%)	0
	CONCERN (>=500 MSEC)	0	0		0
	TOTAL	150	150	(100.0%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
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3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 26/WEEK 92

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (<500 MSEC)	52	51	(98.1%)	1	(1.9%)
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	52	51	(98.1%)	1	(1.9%)
SB 207499	NORMAL (<500 MSEC)	96	95	(99.0%)	1	(1.0%)
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	96	95	(99.0%)	1	(1.0%)
TOTAL	NORMAL (<500 MSEC)	148	146	(98.6%)	2	(1.4%)
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	148	146	(98.6%)	2	(1.4%)

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3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 27/WEEK 96

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (<500 MSEC)	160	159	(99.4%)	1	(0.6%)
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	160	159	(99.4%)	1	(0.6%)
SB 207499	NORMAL (<500 MSEC)	327	326	(99.7%)	1	(0.3%)
	CONCERN (>=500 MSEC)	1	1	(100.0%)	0	
	TOTAL	328	327	(99.7%)	1	(0.3%)
TOTAL	NORMAL (<500 MSEC)	487	485	(99.6%)	2	(0.4%)
	CONCERN (>=500 MSEC)	1	1	(100.0%)	0	
	TOTAL	488	486	(99.6%)	2	(0.4%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 28/WEEK 100

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----		
			NORMAL		CONCERN

PLACEBO	NORMAL (<500 MSEC)	22	22	(100.0%)	0
	CONCERN (>=500 MSEC)	0	0		0
	TOTAL	22	22	(100.0%)	0
SB 207499	NORMAL (<500 MSEC)	49	49	(100.0%)	0
	CONCERN (>=500 MSEC)	0	0		0
	TOTAL	49	49	(100.0%)	0
TOTAL	NORMAL (<500 MSEC)	71	71	(100.0%)	0
	CONCERN (>=500 MSEC)	0	0		0
	TOTAL	71	71	(100.0%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
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3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 29/WEEK 104

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----		
			NORMAL		CONCERN

PLACEBO	NORMAL (<500 MSEC)	18	18	(100.0%)	0
	CONCERN (>=500 MSEC)	0	0		0
	TOTAL	18	18	(100.0%)	0
SB 207499	NORMAL (<500 MSEC)	39	39	(100.0%)	0
	CONCERN (>=500 MSEC)	0	0		0
	TOTAL	39	39	(100.0%)	0
TOTAL	NORMAL (<500 MSEC)	57	57	(100.0%)	0
	CONCERN (>=500 MSEC)	0	0		0
	TOTAL	57	57	(100.0%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 30/WEEK 108

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (<500 MSEC)	126	125	(99.2%)	1	(0.8%)
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	126	125	(99.2%)	1	(0.8%)
SB 207499	NORMAL (<500 MSEC)	272	272	(100.0%)	0	
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	272	272	(100.0%)	0	
TOTAL	NORMAL (<500 MSEC)	398	397	(99.7%)	1	(0.3%)
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	398	397	(99.7%)	1	(0.3%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 31/WEEK 112

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----		
			NORMAL		CONCERN

PLACEBO	NORMAL (<500 MSEC)	9	9	(100.0%)	0
	CONCERN (>=500 MSEC)	0	0		0
	TOTAL	9	9	(100.0%)	0
SB 207499	NORMAL (<500 MSEC)	18	18	(100.0%)	0
	CONCERN (>=500 MSEC)	0	0		0
	TOTAL	18	18	(100.0%)	0
TOTAL	NORMAL (<500 MSEC)	27	27	(100.0%)	0
	CONCERN (>=500 MSEC)	0	0		0
	TOTAL	27	27	(100.0%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 32/WEEK 116

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----		
			NORMAL		CONCERN

PLACEBO	NORMAL (<500 MSEC)	9	9	(100.0%)	0
	CONCERN (>=500 MSEC)	0	0		0
	TOTAL	9	9	(100.0%)	0
SB 207499	NORMAL (<500 MSEC)	15	15	(100.0%)	0
	CONCERN (>=500 MSEC)	0	0		0
	TOTAL	15	15	(100.0%)	0
TOTAL	NORMAL (<500 MSEC)	24	24	(100.0%)	0
	CONCERN (>=500 MSEC)	0	0		0
	TOTAL	24	24	(100.0%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 33/WEEK 120

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (<500 MSEC)	91	90	(98.9%)	1	(1.1%)
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	91	90	(98.9%)	1	(1.1%)
SB 207499	NORMAL (<500 MSEC)	187	187	(100.0%)	0	
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	187	187	(100.0%)	0	
TOTAL	NORMAL (<500 MSEC)	278	277	(99.6%)	1	(0.4%)
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	278	277	(99.6%)	1	(0.4%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 34/WEEK 124

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----		
			NORMAL		CONCERN

PLACEBO	NORMAL (<500 MSEC)	3	3	(100.0%)	0
	CONCERN (>=500 MSEC)	0	0		0
	TOTAL	3	3	(100.0%)	0
SB 207499	NORMAL (<500 MSEC)	3	3	(100.0%)	0
	CONCERN (>=500 MSEC)	0	0		0
	TOTAL	3	3	(100.0%)	0
TOTAL	NORMAL (<500 MSEC)	6	6	(100.0%)	0
	CONCERN (>=500 MSEC)	0	0		0
	TOTAL	6	6	(100.0%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 35/WEEK 128

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----		
			NORMAL		CONCERN

PLACEBO	NORMAL (<500 MSEC)	3	3	(100.0%)	0
	CONCERN (>=500 MSEC)	0	0		0
	TOTAL	3	3	(100.0%)	0
SB 207499	NORMAL (<500 MSEC)	3	3	(100.0%)	0
	CONCERN (>=500 MSEC)	0	0		0
	TOTAL	3	3	(100.0%)	0
TOTAL	NORMAL (<500 MSEC)	6	6	(100.0%)	0
	CONCERN (>=500 MSEC)	0	0		0
	TOTAL	6	6	(100.0%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 36/WEEK 132

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (<500 MSEC)	36	36	(100.0%)	0	
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	36	36	(100.0%)	0	
SB 207499	NORMAL (<500 MSEC)	58	57	(98.3%)	1	(1.7%)
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	58	57	(98.3%)	1	(1.7%)
TOTAL	NORMAL (<500 MSEC)	94	93	(98.9%)	1	(1.1%)
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	94	93	(98.9%)	1	(1.1%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: VISIT 37/WEEK 136

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----		
			NORMAL		CONCERN

PLACEBO	NORMAL (<500 MSEC)	1	1	(100.0%)	0
	CONCERN (>=500 MSEC)	0	0		0
	TOTAL	1	1	(100.0%)	0
SB 207499	NORMAL (<500 MSEC)	2	2	(100.0%)	0
	CONCERN (>=500 MSEC)	0	0		0
	TOTAL	2	2	(100.0%)	0
TOTAL	NORMAL (<500 MSEC)	3	3	(100.0%)	0
	CONCERN (>=500 MSEC)	0	0		0
	TOTAL	3	3	(100.0%)	0

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT		TIME POINT: TOTAL ON-THERAPY			
PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----		
			NORMAL		CONCERN

PLACEBO	NORMAL (<500 MSEC)	239	236	(98.7%)	3 (1.3%)
	CONCERN (>=500 MSEC)	0	0		0
	TOTAL	239	236	(98.7%)	3 (1.3%)
SB 207499	NORMAL (<500 MSEC)	469	463	(98.7%)	6 (1.3%)
	CONCERN (>=500 MSEC)	2	2	(100.0%)	0
	TOTAL	471	465	(98.7%)	6 (1.3%)
TOTAL	NORMAL (<500 MSEC)	708	699	(98.7%)	9 (1.3%)
	CONCERN (>=500 MSEC)	2	2	(100.0%)	0
	TOTAL	710	701	(98.7%)	9 (1.3%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: UNCORRECTED QT TIME POINT: ENDPOINT

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		CONCERN	

PLACEBO	NORMAL (<500 MSEC)	239	238	(99.6%)	1	(0.4%)
	CONCERN (>=500 MSEC)	0	0		0	
	TOTAL	239	238	(99.6%)	1	(0.4%)
SB 207499	NORMAL (<500 MSEC)	469	466	(99.4%)	3	(0.6%)
	CONCERN (>=500 MSEC)	2	2	(100.0%)	0	
	TOTAL	471	468	(99.4%)	3	(0.6%)
TOTAL	NORMAL (<500 MSEC)	708	704	(99.4%)	4	(0.6%)
	CONCERN (>=500 MSEC)	2	2	(100.0%)	0	
	TOTAL	710	706	(99.4%)	4	(0.6%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 2/WEEK 1

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	169	149	(88.2%)	16	(9.5%)	4	(2.4%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	40	20	(50.0%)	14	(35.0%)	6	(15.0%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	25	3	(12.0%)	10	(40.0%)	12	(48.0%)
	TOTAL	234	172	(73.5%)	40	(17.1%)	22	(9.4%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	327	281	(85.9%)	37	(11.3%)	9	(2.8%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	92	41	(44.6%)	35	(38.0%)	16	(17.4%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	43	15	(34.9%)	12	(27.9%)	16	(37.2%)
	TOTAL	462	337	(72.9%)	84	(18.2%)	41	(8.9%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	496	430	(86.7%)	53	(10.7%)	13	(2.6%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	132	61	(46.2%)	49	(37.1%)	22	(16.7%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	68	18	(26.5%)	22	(32.4%)	28	(41.2%)
	TOTAL	696	509	(73.1%)	124	(17.8%)	63	(9.1%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 3/WEEK 2

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	160	138	(86.3%)	16	(10.0%)	6	(3.8%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	39	20	(51.3%)	12	(30.8%)	7	(17.9%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	24	5	(20.8%)	9	(37.5%)	10	(41.7%)
	TOTAL	223	163	(73.1%)	37	(16.6%)	23	(10.3%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	319	276	(86.5%)	37	(11.6%)	6	(1.9%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	89	43	(48.3%)	29	(32.6%)	17	(19.1%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	44	14	(31.8%)	10	(22.7%)	20	(45.5%)
	TOTAL	452	333	(73.7%)	76	(16.8%)	43	(9.5%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	479	414	(86.4%)	53	(11.1%)	12	(2.5%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	128	63	(49.2%)	41	(32.0%)	24	(18.8%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	68	19	(27.9%)	19	(27.9%)	30	(44.1%)
	TOTAL	675	496	(73.5%)	113	(16.7%)	66	(9.8%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 4/WEEK 4

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	153	134	(87.6%)	16	(10.5%)	3	(2.0%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	37	19	(51.4%)	11	(29.7%)	7	(18.9%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	25	7	(28.0%)	5	(20.0%)	13	(52.0%)
	TOTAL	215	160	(74.4%)	32	(14.9%)	23	(10.7%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	326	286	(87.7%)	32	(9.8%)	8	(2.5%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	89	41	(46.1%)	26	(29.2%)	22	(24.7%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	43	11	(25.6%)	14	(32.6%)	18	(41.9%)
	TOTAL	458	338	(73.8%)	72	(15.7%)	48	(10.5%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	479	420	(87.7%)	48	(10.0%)	11	(2.3%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	126	60	(47.6%)	37	(29.4%)	29	(23.0%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	68	18	(26.5%)	19	(27.9%)	31	(45.6%)
	TOTAL	673	498	(74.0%)	104	(15.5%)	71	(10.5%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 5/WEEK 8

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	151	134	(88.7%)	11	(7.3%)	6	(4.0%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	38	21	(55.3%)	14	(36.8%)	3	(7.9%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	24	5	(20.8%)	10	(41.7%)	9	(37.5%)
	TOTAL	213	160	(75.1%)	35	(16.4%)	18	(8.5%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	317	278	(87.7%)	35	(11.0%)	4	(1.3%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	87	41	(47.1%)	27	(31.0%)	19	(21.8%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	43	11	(25.6%)	13	(30.2%)	19	(44.2%)
	TOTAL	447	330	(73.8%)	75	(16.8%)	42	(9.4%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	468	412	(88.0%)	46	(9.8%)	10	(2.1%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	125	62	(49.6%)	41	(32.8%)	22	(17.6%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	67	16	(23.9%)	23	(34.3%)	28	(41.8%)
	TOTAL	660	490	(74.2%)	110	(16.7%)	60	(9.1%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 6/WEEK 12

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	148	125	(84.5%)	18	(12.2%)	5	(3.4%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	38	13	(34.2%)	17	(44.7%)	8	(21.1%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	22	4	(18.2%)	8	(36.4%)	10	(45.5%)
	TOTAL	208	142	(68.3%)	43	(20.7%)	23	(11.1%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	313	270	(86.3%)	37	(11.8%)	6	(1.9%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	88	40	(45.5%)	30	(34.1%)	18	(20.5%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	43	14	(32.6%)	9	(20.9%)	20	(46.5%)
	TOTAL	444	324	(73.0%)	76	(17.1%)	44	(9.9%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	461	395	(85.7%)	55	(11.9%)	11	(2.4%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	126	53	(42.1%)	47	(37.3%)	26	(20.6%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	65	18	(27.7%)	17	(26.2%)	30	(46.2%)
	TOTAL	652	466	(71.5%)	119	(18.3%)	67	(10.3%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 7/WEEK 16

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	144	122	(84.7%)	19	(13.2%)	3	(2.1%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	37	15	(40.5%)	15	(40.5%)	7	(18.9%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	21	7	(33.3%)	5	(23.8%)	9	(42.9%)
	TOTAL	202	144	(71.3%)	39	(19.3%)	19	(9.4%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	308	274	(89.0%)	29	(9.4%)	5	(1.6%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	87	37	(42.5%)	30	(34.5%)	20	(23.0%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	41	13	(31.7%)	12	(29.3%)	16	(39.0%)
	TOTAL	436	324	(74.3%)	71	(16.3%)	41	(9.4%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	452	396	(87.6%)	48	(10.6%)	8	(1.8%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	124	52	(41.9%)	45	(36.3%)	27	(21.8%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	62	20	(32.3%)	17	(27.4%)	25	(40.3%)
	TOTAL	638	468	(73.4%)	110	(17.2%)	60	(9.4%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 8/WEEK 20

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	142	117	(82.4%)	19	(13.4%)	6	(4.2%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	36	16	(44.4%)	14	(38.9%)	6	(16.7%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	19	4	(21.1%)	5	(26.3%)	10	(52.6%)
	TOTAL	197	137	(69.5%)	38	(19.3%)	22	(11.2%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	307	276	(89.9%)	24	(7.8%)	7	(2.3%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	85	41	(48.2%)	25	(29.4%)	19	(22.4%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	40	7	(17.5%)	15	(37.5%)	18	(45.0%)
	TOTAL	432	324	(75.0%)	64	(14.8%)	44	(10.2%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	449	393	(87.5%)	43	(9.6%)	13	(2.9%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	121	57	(47.1%)	39	(32.2%)	25	(20.7%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	59	11	(18.6%)	20	(33.9%)	28	(47.5%)
	TOTAL	629	461	(73.3%)	102	(16.2%)	66	(10.5%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 9/WEEK 24

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	138	117	(84.8%)	17	(12.3%)	4	(2.9%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	36	22	(61.1%)	9	(25.0%)	5	(13.9%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	19	4	(21.1%)	5	(26.3%)	10	(52.6%)
	TOTAL	193	143	(74.1%)	31	(16.1%)	19	(9.8%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	306	263	(85.9%)	39	(12.7%)	4	(1.3%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	80	34	(42.5%)	28	(35.0%)	18	(22.5%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	41	10	(24.4%)	15	(36.6%)	16	(39.0%)
	TOTAL	427	307	(71.9%)	82	(19.2%)	38	(8.9%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	444	380	(85.6%)	56	(12.6%)	8	(1.8%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	116	56	(48.3%)	37	(31.9%)	23	(19.8%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	60	14	(23.3%)	20	(33.3%)	26	(43.3%)
	TOTAL	620	450	(72.6%)	113	(18.2%)	57	(9.2%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 10/WEEK 28

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	135	117	(86.7%)	12	(8.9%)	6	(4.4%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	35	19	(54.3%)	7	(20.0%)	9	(25.7%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	20	3	(15.0%)	4	(20.0%)	13	(65.0%)
	TOTAL	190	139	(73.2%)	23	(12.1%)	28	(14.7%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	300	266	(88.7%)	31	(10.3%)	3	(1.0%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	81	29	(35.8%)	34	(42.0%)	18	(22.2%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	41	13	(31.7%)	11	(26.8%)	17	(41.5%)
	TOTAL	422	308	(73.0%)	76	(18.0%)	38	(9.0%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	435	383	(88.0%)	43	(9.9%)	9	(2.1%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	116	48	(41.4%)	41	(35.3%)	27	(23.3%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	61	16	(26.2%)	15	(24.6%)	30	(49.2%)
	TOTAL	612	447	(73.0%)	99	(16.2%)	66	(10.8%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 11/WEEK 32

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	135	120	(88.9%)	9	(6.7%)	6	(4.4%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	33	16	(48.5%)	10	(30.3%)	7	(21.2%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	18	1	(5.6%)	8	(44.4%)	9	(50.0%)
	TOTAL	186	137	(73.7%)	27	(14.5%)	22	(11.8%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	299	264	(88.3%)	26	(8.7%)	9	(3.0%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	80	33	(41.3%)	31	(38.8%)	16	(20.0%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	40	12	(30.0%)	11	(27.5%)	17	(42.5%)
	TOTAL	419	309	(73.7%)	68	(16.2%)	42	(10.0%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	434	384	(88.5%)	35	(8.1%)	15	(3.5%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	113	49	(43.4%)	41	(36.3%)	23	(20.4%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	58	13	(22.4%)	19	(32.8%)	26	(44.8%)
	TOTAL	605	446	(73.7%)	95	(15.7%)	64	(10.6%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 12/WEEK 36

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	135	113	(83.7%)	14	(10.4%)	8	(5.9%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	34	18	(52.9%)	12	(35.3%)	4	(11.8%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	18	4	(22.2%)	7	(38.9%)	7	(38.9%)
	TOTAL	187	135	(72.2%)	33	(17.6%)	19	(10.2%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	292	258	(88.4%)	31	(10.6%)	3	(1.0%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	79	38	(48.1%)	24	(30.4%)	17	(21.5%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	39	13	(33.3%)	12	(30.8%)	14	(35.9%)
	TOTAL	410	309	(75.4%)	67	(16.3%)	34	(8.3%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	427	371	(86.9%)	45	(10.5%)	11	(2.6%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	113	56	(49.6%)	36	(31.9%)	21	(18.6%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	57	17	(29.8%)	19	(33.3%)	21	(36.8%)
	TOTAL	597	444	(74.4%)	100	(16.8%)	53	(8.9%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 13/WEEK 40

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	134	111	(82.8%)	19	(14.2%)	4	(3.0%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	33	14	(42.4%)	14	(42.4%)	5	(15.2%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	18	5	(27.8%)	6	(33.3%)	7	(38.9%)
	TOTAL	185	130	(70.3%)	39	(21.1%)	16	(8.6%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	287	253	(88.2%)	30	(10.5%)	4	(1.4%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	78	35	(44.9%)	25	(32.1%)	18	(23.1%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	40	10	(25.0%)	15	(37.5%)	15	(37.5%)
	TOTAL	405	298	(73.6%)	70	(17.3%)	37	(9.1%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	421	364	(86.5%)	49	(11.6%)	8	(1.9%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	111	49	(44.1%)	39	(35.1%)	23	(20.7%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	58	15	(25.9%)	21	(36.2%)	22	(37.9%)
	TOTAL	590	428	(72.5%)	109	(18.5%)	53	(9.0%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 14/WEEK 44

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	132	112	(84.8%)	17	(12.9%)	3	(2.3%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	33	15	(45.5%)	14	(42.4%)	4	(12.1%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	18	5	(27.8%)	5	(27.8%)	8	(44.4%)
	TOTAL	183	132	(72.1%)	36	(19.7%)	15	(8.2%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	288	241	(83.7%)	39	(13.5%)	8	(2.8%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	77	35	(45.5%)	23	(29.9%)	19	(24.7%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	39	10	(25.6%)	13	(33.3%)	16	(41.0%)
	TOTAL	404	286	(70.8%)	75	(18.6%)	43	(10.6%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	420	353	(84.0%)	56	(13.3%)	11	(2.6%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	110	50	(45.5%)	37	(33.6%)	23	(20.9%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	57	15	(26.3%)	18	(31.6%)	24	(42.1%)
	TOTAL	587	418	(71.2%)	111	(18.9%)	58	(9.9%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 15/WEEK 48

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	133	110	(82.7%)	20	(15.0%)	3	(2.3%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	33	17	(51.5%)	11	(33.3%)	5	(15.2%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	18	5	(27.8%)	7	(38.9%)	6	(33.3%)
	TOTAL	184	132	(71.7%)	38	(20.7%)	14	(7.6%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	283	250	(88.3%)	29	(10.2%)	4	(1.4%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	74	33	(44.6%)	26	(35.1%)	15	(20.3%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	39	10	(25.6%)	10	(25.6%)	19	(48.7%)
	TOTAL	396	293	(74.0%)	65	(16.4%)	38	(9.6%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	416	360	(86.5%)	49	(11.8%)	7	(1.7%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	107	50	(46.7%)	37	(34.6%)	20	(18.7%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	57	15	(26.3%)	17	(29.8%)	25	(43.9%)
	TOTAL	580	425	(73.3%)	103	(17.8%)	52	(9.0%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 16/WEEK 52

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	130	112	(86.2%)	15	(11.5%)	3	(2.3%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	33	11	(33.3%)	14	(42.4%)	8	(24.2%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	17	3	(17.6%)	9	(52.9%)	5	(29.4%)
	TOTAL	180	126	(70.0%)	38	(21.1%)	16	(8.9%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	274	235	(85.8%)	33	(12.0%)	6	(2.2%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	70	27	(38.6%)	33	(47.1%)	10	(14.3%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	39	16	(41.0%)	8	(20.5%)	15	(38.5%)
	TOTAL	383	278	(72.6%)	74	(19.3%)	31	(8.1%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	404	347	(85.9%)	48	(11.9%)	9	(2.2%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	103	38	(36.9%)	47	(45.6%)	18	(17.5%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	56	19	(33.9%)	17	(30.4%)	20	(35.7%)
	TOTAL	563	404	(71.8%)	112	(19.9%)	47	(8.3%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 17/WEEK 56

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	121	102	(84.3%)	15	(12.4%)	4	(3.3%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	33	14	(42.4%)	10	(30.3%)	9	(27.3%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	15	4	(26.7%)	3	(20.0%)	8	(53.3%)
	TOTAL	169	120	(71.0%)	28	(16.6%)	21	(12.4%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	259	226	(87.3%)	27	(10.4%)	6	(2.3%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	68	29	(42.6%)	28	(41.2%)	11	(16.2%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	37	11	(29.7%)	9	(24.3%)	17	(45.9%)
	TOTAL	364	266	(73.1%)	64	(17.6%)	34	(9.3%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	380	328	(86.3%)	42	(11.1%)	10	(2.6%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	101	43	(42.6%)	38	(37.6%)	20	(19.8%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	52	15	(28.8%)	12	(23.1%)	25	(48.1%)
	TOTAL	533	386	(72.4%)	92	(17.3%)	55	(10.3%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 18/WEEK 60

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	124	99	(79.8%)	19	(15.3%)	6	(4.8%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	32	13	(40.6%)	13	(40.6%)	6	(18.8%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	17	5	(29.4%)	4	(23.5%)	8	(47.1%)
	TOTAL	173	117	(67.6%)	36	(20.8%)	20	(11.6%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	265	226	(85.3%)	34	(12.8%)	5	(1.9%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	70	26	(37.1%)	32	(45.7%)	12	(17.1%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	38	13	(34.2%)	7	(18.4%)	18	(47.4%)
	TOTAL	373	265	(71.0%)	73	(19.6%)	35	(9.4%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	389	325	(83.5%)	53	(13.6%)	11	(2.8%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	102	39	(38.2%)	45	(44.1%)	18	(17.6%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	55	18	(32.7%)	11	(20.0%)	26	(47.3%)
	TOTAL	546	382	(70.0%)	109	(20.0%)	55	(10.1%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 19/WEEK 64

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	104	87	(83.7%)	13	(12.5%)	4	(3.8%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	25	17	(68.0%)	4	(16.0%)	4	(16.0%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	13	4	(30.8%)	6	(46.2%)	3	(23.1%)
	TOTAL	142	108	(76.1%)	23	(16.2%)	11	(7.7%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	219	187	(85.4%)	23	(10.5%)	9	(4.1%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	58	26	(44.8%)	24	(41.4%)	8	(13.8%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	31	7	(22.6%)	9	(29.0%)	15	(48.4%)
	TOTAL	308	220	(71.4%)	56	(18.2%)	32	(10.4%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	323	274	(84.8%)	36	(11.1%)	13	(4.0%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	83	43	(51.8%)	28	(33.7%)	12	(14.5%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	44	11	(25.0%)	15	(34.1%)	18	(40.9%)
	TOTAL	450	328	(72.9%)	79	(17.6%)	43	(9.6%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 20/WEEK 68

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	102	83	(81.4%)	14	(13.7%)	5	(4.9%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	25	13	(52.0%)	9	(36.0%)	3	(12.0%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	13	5	(38.5%)	5	(38.5%)	3	(23.1%)
	TOTAL	140	101	(72.1%)	28	(20.0%)	11	(7.9%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	209	179	(85.6%)	22	(10.5%)	8	(3.8%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	57	21	(36.8%)	23	(40.4%)	13	(22.8%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	29	6	(20.7%)	9	(31.0%)	14	(48.3%)
	TOTAL	295	206	(69.8%)	54	(18.3%)	35	(11.9%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	311	262	(84.2%)	36	(11.6%)	13	(4.2%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	82	34	(41.5%)	32	(39.0%)	16	(19.5%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	42	11	(26.2%)	14	(33.3%)	17	(40.5%)
	TOTAL	435	307	(70.6%)	82	(18.9%)	46	(10.6%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 21/WEEK 72

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	122	103	(84.4%)	15	(12.3%)	4	(3.3%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	31	17	(54.8%)	9	(29.0%)	5	(16.1%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	17	5	(29.4%)	8	(47.1%)	4	(23.5%)
	TOTAL	170	125	(73.5%)	32	(18.8%)	13	(7.6%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	254	217	(85.4%)	32	(12.6%)	5	(2.0%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	66	25	(37.9%)	25	(37.9%)	16	(24.2%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	37	9	(24.3%)	8	(21.6%)	20	(54.1%)
	TOTAL	357	251	(70.3%)	65	(18.2%)	41	(11.5%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	376	320	(85.1%)	47	(12.5%)	9	(2.4%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	97	42	(43.3%)	34	(35.1%)	21	(21.6%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	54	14	(25.9%)	16	(29.6%)	24	(44.4%)
	TOTAL	527	376	(71.3%)	97	(18.4%)	54	(10.2%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 22/WEEK 76

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	73	66	(90.4%)	4	(5.5%)	3	(4.1%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	18	11	(61.1%)	3	(16.7%)	4	(22.2%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	9	2	(22.2%)	2	(22.2%)	5	(55.6%)
	TOTAL	100	79	(79.0%)	9	(9.0%)	12	(12.0%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	148	125	(84.5%)	21	(14.2%)	2	(1.4%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	37	13	(35.1%)	16	(43.2%)	8	(21.6%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	13	4	(30.8%)	5	(38.5%)	4	(30.8%)
	TOTAL	198	142	(71.7%)	42	(21.2%)	14	(7.1%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	221	191	(86.4%)	25	(11.3%)	5	(2.3%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	55	24	(43.6%)	19	(34.5%)	12	(21.8%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	22	6	(27.3%)	7	(31.8%)	9	(40.9%)
	TOTAL	298	221	(74.2%)	51	(17.1%)	26	(8.7%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 23/WEEK 80

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	72	64	(88.9%)	6	(8.3%)	2	(2.8%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	17	12	(70.6%)	2	(11.8%)	3	(17.6%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	9	4	(44.4%)	0		5	(55.6%)
	TOTAL	98	80	(81.6%)	8	(8.2%)	10	(10.2%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	147	122	(83.0%)	17	(11.6%)	8	(5.4%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	34	15	(44.1%)	13	(38.2%)	6	(17.6%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	12	2	(16.7%)	5	(41.7%)	5	(41.7%)
	TOTAL	193	139	(72.0%)	35	(18.1%)	19	(9.8%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	219	186	(84.9%)	23	(10.5%)	10	(4.6%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	51	27	(52.9%)	15	(29.4%)	9	(17.6%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	21	6	(28.6%)	5	(23.8%)	10	(47.6%)
	TOTAL	291	219	(75.3%)	43	(14.8%)	29	(10.0%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 24/WEEK 84

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	118	99	(83.9%)	12	(10.2%)	7	(5.9%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	30	14	(46.7%)	15	(50.0%)	1	(3.3%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	15	3	(20.0%)	7	(46.7%)	5	(33.3%)
	TOTAL	163	116	(71.2%)	34	(20.9%)	13	(8.0%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	240	208	(86.7%)	29	(12.1%)	3	(1.3%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	59	22	(37.3%)	26	(44.1%)	11	(18.6%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	35	10	(28.6%)	9	(25.7%)	16	(45.7%)
	TOTAL	334	240	(71.9%)	64	(19.2%)	30	(9.0%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	358	307	(85.8%)	41	(11.5%)	10	(2.8%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	89	36	(40.4%)	41	(46.1%)	12	(13.5%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	50	13	(26.0%)	16	(32.0%)	21	(42.0%)
	TOTAL	497	356	(71.6%)	98	(19.7%)	43	(8.7%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 25/WEEK 88

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	43	39	(90.7%)	3	(7.0%)	1	(2.3%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	7	4	(57.1%)	2	(28.6%)	1	(14.3%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	3	1	(33.3%)	1	(33.3%)	1	(33.3%)
	TOTAL	53	44	(83.0%)	6	(11.3%)	3	(5.7%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	76	69	(90.8%)	6	(7.9%)	1	(1.3%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	17	5	(29.4%)	11	(64.7%)	1	(5.9%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	4	2	(50.0%)	1	(25.0%)	1	(25.0%)
	TOTAL	97	76	(78.4%)	18	(18.6%)	3	(3.1%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	119	108	(90.8%)	9	(7.6%)	2	(1.7%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	24	9	(37.5%)	13	(54.2%)	2	(8.3%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	7	3	(42.9%)	2	(28.6%)	2	(28.6%)
	TOTAL	150	120	(80.0%)	24	(16.0%)	6	(4.0%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 26/WEEK 92

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	42	36	(85.7%)	2	(4.8%)	4	(9.5%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	7	5	(71.4%)	1	(14.3%)	1	(14.3%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	3	2	(66.7%)	0		1	(33.3%)
	TOTAL	52	43	(82.7%)	3	(5.8%)	6	(11.5%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	75	65	(86.7%)	8	(10.7%)	2	(2.7%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	17	4	(23.5%)	9	(52.9%)	4	(23.5%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	4	2	(50.0%)	1	(25.0%)	1	(25.0%)
	TOTAL	96	71	(74.0%)	18	(18.8%)	7	(7.3%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	117	101	(86.3%)	10	(8.5%)	6	(5.1%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	24	9	(37.5%)	10	(41.7%)	5	(20.8%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	7	4	(57.1%)	1	(14.3%)	2	(28.6%)
	TOTAL	148	114	(77.0%)	21	(14.2%)	13	(8.8%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 27/WEEK 96

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	114	94	(82.5%)	18	(15.8%)	2	(1.8%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	30	14	(46.7%)	9	(30.0%)	7	(23.3%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	16	2	(12.5%)	4	(25.0%)	10	(62.5%)
	TOTAL	160	110	(68.8%)	31	(19.4%)	19	(11.9%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	233	193	(82.8%)	32	(13.7%)	8	(3.4%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	59	23	(39.0%)	21	(35.6%)	15	(25.4%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	36	7	(19.4%)	12	(33.3%)	17	(47.2%)
	TOTAL	328	223	(68.0%)	65	(19.8%)	40	(12.2%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	347	287	(82.7%)	50	(14.4%)	10	(2.9%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	89	37	(41.6%)	30	(33.7%)	22	(24.7%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	52	9	(17.3%)	16	(30.8%)	27	(51.9%)
	TOTAL	488	333	(68.2%)	96	(19.7%)	59	(12.1%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 28/WEEK 100

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	19	18	(94.7%)	1	(5.3%)	0
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	2	1	(50.0%)	0		1 (50.0%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	1	0		0		1 (100.0%)
	TOTAL	22	19	(86.4%)	1	(4.5%)	2 (9.1%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	38	32	(84.2%)	4	(10.5%)	2 (5.3%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	10	3	(30.0%)	6	(60.0%)	1 (10.0%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	1	0		1	(100.0%)	0
	TOTAL	49	35	(71.4%)	11	(22.4%)	3 (6.1%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	57	50	(87.7%)	5	(8.8%)	2 (3.5%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	12	4	(33.3%)	6	(50.0%)	2 (16.7%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	2	0		1	(50.0%)	1 (50.0%)
	TOTAL	71	54	(76.1%)	12	(16.9%)	5 (7.0%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 29/WEEK 104

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL		HIGH		CONCERN
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	16	13	(81.3%)	3	(18.8%)	0
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	2	2	(100.0%)	0		0
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0		0		0
	TOTAL	18	15	(83.3%)	3	(16.7%)	0
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	29	24	(82.8%)	3	(10.3%)	2 (6.9%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	10	3	(30.0%)	6	(60.0%)	1 (10.0%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0		0		0
	TOTAL	39	27	(69.2%)	9	(23.1%)	3 (7.7%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	45	37	(82.2%)	6	(13.3%)	2 (4.4%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	12	5	(41.7%)	6	(50.0%)	1 (8.3%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0		0		0
	TOTAL	57	42	(73.7%)	12	(21.1%)	3 (5.3%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 30/WEEK 108

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	88	70	(79.5%)	12	(13.6%)	6	(6.8%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	25	9	(36.0%)	11	(44.0%)	5	(20.0%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	13	3	(23.1%)	5	(38.5%)	5	(38.5%)
	TOTAL	126	82	(65.1%)	28	(22.2%)	16	(12.7%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	191	162	(84.8%)	23	(12.0%)	6	(3.1%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	48	19	(39.6%)	21	(43.8%)	8	(16.7%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	33	8	(24.2%)	10	(30.3%)	15	(45.5%)
	TOTAL	272	189	(69.5%)	54	(19.9%)	29	(10.7%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	279	232	(83.2%)	35	(12.5%)	12	(4.3%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	73	28	(38.4%)	32	(43.8%)	13	(17.8%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	46	11	(23.9%)	15	(32.6%)	20	(43.5%)
	TOTAL	398	271	(68.1%)	82	(20.6%)	45	(11.3%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 31/WEEK 112

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL	HIGH	CONCERN	
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	8	8 (100.0%)	0	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	1	1 (100.0%)	0	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0	0	0	
	TOTAL	9	9 (100.0%)	0	0	
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	10	9 (90.0%)	1 (10.0%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	8	3 (37.5%)	3 (37.5%)	2 (25.0%)	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0	0	0	
	TOTAL	18	12 (66.7%)	4 (22.2%)	2 (11.1%)	
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	18	17 (94.4%)	1 (5.6%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	9	4 (44.4%)	3 (33.3%)	2 (22.2%)	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0	0	0	
	TOTAL	27	21 (77.8%)	4 (14.8%)	2 (7.4%)	

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 32/WEEK 116

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL	HIGH	CONCERN	
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	8	6 (75.0%)	1 (12.5%)	1 (12.5%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	1	1 (100.0%)	0	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0	0	0	
	TOTAL	9	7 (77.8%)	1 (11.1%)	1 (11.1%)	
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	8	7 (87.5%)	1 (12.5%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	7	3 (42.9%)	2 (28.6%)	2 (28.6%)	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0	0	0	
	TOTAL	15	10 (66.7%)	3 (20.0%)	2 (13.3%)	
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	16	13 (81.3%)	2 (12.5%)	1 (6.3%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	8	4 (50.0%)	2 (25.0%)	2 (25.0%)	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0	0	0	
	TOTAL	24	17 (70.8%)	4 (16.7%)	3 (12.5%)	

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 33/WEEK 120

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	66	57	(86.4%)	8	(12.1%)	1	(1.5%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	16	7	(43.8%)	5	(31.3%)	4	(25.0%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	9	0		5	(55.6%)	4	(44.4%)
	TOTAL	91	64	(70.3%)	18	(19.8%)	9	(9.9%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	132	110	(83.3%)	19	(14.4%)	3	(2.3%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	34	14	(41.2%)	11	(32.4%)	9	(26.5%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	21	5	(23.8%)	6	(28.6%)	10	(47.6%)
	TOTAL	187	129	(69.0%)	36	(19.3%)	22	(11.8%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	198	167	(84.3%)	27	(13.6%)	4	(2.0%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	50	21	(42.0%)	16	(32.0%)	13	(26.0%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	30	5	(16.7%)	11	(36.7%)	14	(46.7%)
	TOTAL	278	193	(69.4%)	54	(19.4%)	31	(11.2%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 34/WEEK 124

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		HIGH	CONCERN
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	3	2 (66.7%)	1 (33.3%)	0	
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	0	0	0	0	
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0	0	0	
	TOTAL	3	2 (66.7%)	1 (33.3%)	0	
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	2	1 (50.0%)	1 (50.0%)	0	
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	1	0	0	1 (100.0%)	
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0	0	0	
	TOTAL	3	1 (33.3%)	1 (33.3%)	1 (33.3%)	
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	5	3 (60.0%)	2 (40.0%)	0	
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	1	0	0	1 (100.0%)	
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0	0	0	
	TOTAL	6	3 (50.0%)	2 (33.3%)	1 (16.7%)	

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 35/WEEK 128

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL		HIGH	CONCERN
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	3	1 (33.3%)		2 (66.7%)	0
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	0	0		0	0
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0		0	0
	TOTAL	3	1 (33.3%)		2 (66.7%)	0
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	2	2 (100.0%)		0	0
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	1	0		0	1 (100.0%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0		0	0
	TOTAL	3	2 (66.7%)		0	1 (33.3%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	5	3 (60.0%)		2 (40.0%)	0
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	1	0		0	1 (100.0%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0		0	0
	TOTAL	6	3 (50.0%)		2 (33.3%)	1 (16.7%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 36/WEEK 132

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	28	22	(78.6%)	4	(14.3%)	2	(7.1%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	5	3	(60.0%)	2	(40.0%)	0	
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	3	1	(33.3%)	1	(33.3%)	1	(33.3%)
	TOTAL	36	26	(72.2%)	7	(19.4%)	3	(8.3%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	40	35	(87.5%)	4	(10.0%)	1	(2.5%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	16	3	(18.8%)	6	(37.5%)	7	(43.8%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	2	0		0		2	(100.0%)
	TOTAL	58	38	(65.5%)	10	(17.2%)	10	(17.2%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	68	57	(83.8%)	8	(11.8%)	3	(4.4%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	21	6	(28.6%)	8	(38.1%)	7	(33.3%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	5	1	(20.0%)	1	(20.0%)	3	(60.0%)
	TOTAL	94	64	(68.1%)	17	(18.1%)	13	(13.8%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: VISIT 37/WEEK 136

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL	HIGH	CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	1	1 (100.0%)	0	0	
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	0	0	0	0	
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0	0	0	
	TOTAL	1	1 (100.0%)	0	0	
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	2	2 (100.0%)	0	0	
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	0	0	0	0	
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0	0	0	
	TOTAL	2	2 (100.0%)	0	0	
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	3	3 (100.0%)	0	0	
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	0	0	0	0	
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0	0	0	
	TOTAL	3	3 (100.0%)	0	0	

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: CORRECTED QT TIME POINT: TOTAL ON-THERAPY

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL		HIGH		CONCERN	
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	174	82	(47.1%)	56	(32.2%)	36	(20.7%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	40	2	(5.0%)	8	(20.0%)	30	(75.0%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	25	0		3	(12.0%)	22	(88.0%)
	TOTAL	239	84	(35.1%)	67	(28.0%)	88	(36.8%)
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	334	148	(44.3%)	119	(35.6%)	67	(20.1%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	93	5	(5.4%)	19	(20.4%)	69	(74.2%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	44	3	(6.8%)	7	(15.9%)	34	(77.3%)
	TOTAL	471	156	(33.1%)	145	(30.8%)	170	(36.1%)
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	508	230	(45.3%)	175	(34.4%)	103	(20.3%)
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	133	7	(5.3%)	27	(20.3%)	99	(74.4%)
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	69	3	(4.3%)	10	(14.5%)	56	(81.2%)
	TOTAL	710	240	(33.8%)	212	(29.9%)	258	(36.3%)

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19A

TRANSITIONS FROM BASELINE IN ECG PARAMETERS BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

		PARAMETER: CORRECTED QT		TIME POINT: ENDPOINT					
PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----NORMAL-----		-----ON-THERAPY-----		-----HIGH-----		-----CONCERN-----
PLACEBO	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	174	144	(82.8%)	24	(13.8%)	6	(3.4%)	
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	40	14	(35.0%)	16	(40.0%)	10	(25.0%)	
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	25	3	(12.0%)	12	(48.0%)	10	(40.0%)	
	TOTAL	239	161	(67.4%)	52	(21.8%)	26	(10.9%)	
SB 207499	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	334	277	(82.9%)	46	(13.8%)	11	(3.3%)	
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	93	37	(39.8%)	32	(34.4%)	24	(25.8%)	
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	44	12	(27.3%)	14	(31.8%)	18	(40.9%)	
	TOTAL	471	326	(69.2%)	92	(19.5%)	53	(11.3%)	
TOTAL	NORMAL(<430 MSEC [MALE] AND <450 MSEC [FEMALE])	508	421	(82.9%)	70	(13.8%)	17	(3.3%)	
	HIGH(430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	133	51	(38.3%)	48	(36.1%)	34	(25.6%)	
	CONCERN(>450 MSEC [MALE] AND >470 MSEC [FEMALE])	69	15	(21.7%)	26	(37.7%)	28	(40.6%)	
	TOTAL	710	487	(68.6%)	144	(20.3%)	79	(11.1%)	

1. PATIENTS WITH ON-THERAPY VALUES WHO MEET CRITERIA FOR BOTH HIGH AND LOW VALUES OF INTEREST AND CONCERN ARE REPORTED IN BOTH CATEGORIES, IF APPLICABLE
2. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST AND/OR LOWEST ON-THERAPY VALUE
3. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
4. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
5. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

SB 207499

TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 2/WEEK 1

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL (<30 MSEC)	HIGH (30-60 MSEC)	CONCERN (>60 MSEC)	
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	169	159 (94.1%)	7 (4.1%)	3 (1.8%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	40	39 (97.5%)	1 (2.5%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	25	25 (100.0%)	0	0	
	TOTAL	234	223 (95.3%)	8 (3.4%)	3 (1.3%)	
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	327	314 (96.0%)	11 (3.4%)	2 (0.6%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	92	89 (96.7%)	3 (3.3%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	43	42 (97.7%)	1 (2.3%)	0	
	TOTAL	462	445 (96.3%)	15 (3.2%)	2 (0.4%)	
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	496	473 (95.4%)	18 (3.6%)	5 (1.0%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	132	128 (97.0%)	4 (3.0%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	68	67 (98.5%)	1 (1.5%)	0	
	TOTAL	696	668 (96.0%)	23 (3.3%)	5 (0.7%)	

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 3/WEEK 2

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL (<30 MSEC)		HIGH (30-60 MSEC)		CONCERN (>60 MSEC)	
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	160	149	(93.1%)	10	(6.3%)	1	(0.6%)
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	39	38	(97.4%)	1	(2.6%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	24	23	(95.8%)	1	(4.2%)	0	
	TOTAL	223	210	(94.2%)	12	(5.4%)	1	(0.4%)
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	319	309	(96.9%)	10	(3.1%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	89	84	(94.4%)	5	(5.6%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	44	43	(97.7%)	1	(2.3%)	0	
	TOTAL	452	436	(96.5%)	16	(3.5%)	0	
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	479	458	(95.6%)	20	(4.2%)	1	(0.2%)
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	128	122	(95.3%)	6	(4.7%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	68	66	(97.1%)	2	(2.9%)	0	
	TOTAL	675	646	(95.7%)	28	(4.1%)	1	(0.1%)

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

SB 207499

TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 4/WEEK 4

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL (<30 MSEC)		HIGH (30-60 MSEC)		CONCERN (>60 MSEC)	
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	153	143	(93.5%)	9	(5.9%)	1	(0.7%)
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	37	36	(97.3%)	1	(2.7%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	25	25	(100.0%)	0		0	
	TOTAL	215	204	(94.9%)	10	(4.7%)	1	(0.5%)
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	326	314	(96.3%)	10	(3.1%)	2	(0.6%)
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	89	86	(96.6%)	3	(3.4%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	43	42	(97.7%)	1	(2.3%)	0	
	TOTAL	458	442	(96.5%)	14	(3.1%)	2	(0.4%)
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	479	457	(95.4%)	19	(4.0%)	3	(0.6%)
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	126	122	(96.8%)	4	(3.2%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	68	67	(98.5%)	1	(1.5%)	0	
	TOTAL	673	646	(96.0%)	24	(3.6%)	3	(0.4%)

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 5/WEEK 8

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL (<30 MSEC)	HIGH (30-60 MSEC)	CONCERN (>60 MSEC)	
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	151	140 (92.7%)	11 (7.3%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	38	37 (97.4%)	1 (2.6%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	24	24 (100.0%)	0	0	
	TOTAL	213	201 (94.4%)	12 (5.6%)	0	
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	317	307 (96.8%)	10 (3.2%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	87	83 (95.4%)	4 (4.6%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	43	42 (97.7%)	0	1 (2.3%)	
	TOTAL	447	432 (96.6%)	14 (3.1%)	1 (0.2%)	
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	468	447 (95.5%)	21 (4.5%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	125	120 (96.0%)	5 (4.0%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	67	66 (98.5%)	0	1 (1.5%)	
	TOTAL	660	633 (95.9%)	26 (3.9%)	1 (0.2%)	

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 6/WEEK 12

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL (<30 MSEC)		HIGH (30-60 MSEC)		CONCERN (>60 MSEC)	
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	148	137	(92.6%)	8	(5.4%)	3	(2.0%)
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	38	35	(92.1%)	3	(7.9%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	22	22	(100.0%)	0		0	
	TOTAL	208	194	(93.3%)	11	(5.3%)	3	(1.4%)
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	313	298	(95.2%)	15	(4.8%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	88	84	(95.5%)	4	(4.5%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	43	41	(95.3%)	2	(4.7%)	0	
	TOTAL	444	423	(95.3%)	21	(4.7%)	0	
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	461	435	(94.4%)	23	(5.0%)	3	(0.7%)
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	126	119	(94.4%)	7	(5.6%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	65	63	(96.9%)	2	(3.1%)	0	
	TOTAL	652	617	(94.6%)	32	(4.9%)	3	(0.5%)

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

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TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 7/WEEK 16

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL (<30 MSEC)	HIGH (30-60 MSEC)	CONCERN (>60 MSEC)	
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	144	138 (95.8%)	6 (4.2%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	37	35 (94.6%)	2 (5.4%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	21	21 (100.0%)	0	0	
	TOTAL	202	194 (96.0%)	8 (4.0%)	0	
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	308	300 (97.4%)	7 (2.3%)	1 (0.3%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	87	83 (95.4%)	3 (3.4%)	1 (1.1%)	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	41	41 (100.0%)	0	0	
	TOTAL	436	424 (97.2%)	10 (2.3%)	2 (0.5%)	
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	452	438 (96.9%)	13 (2.9%)	1 (0.2%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	124	118 (95.2%)	5 (4.0%)	1 (0.8%)	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	62	62 (100.0%)	0	0	
	TOTAL	638	618 (96.9%)	18 (2.8%)	2 (0.3%)	

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

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TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 8/WEEK 20

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL (<30 MSEC)	HIGH (30-60 MSEC)	CONCERN (>60 MSEC)	
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	142	131 (92.3%)	11 (7.7%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	36	35 (97.2%)	0	1 (2.8%)	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	19	19 (100.0%)	0	0	
	TOTAL	197	185 (93.9%)	11 (5.6%)	1 (0.5%)	
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	307	294 (95.8%)	12 (3.9%)	1 (0.3%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	85	83 (97.6%)	2 (2.4%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	40	39 (97.5%)	1 (2.5%)	0	
	TOTAL	432	416 (96.3%)	15 (3.5%)	1 (0.2%)	
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	449	425 (94.7%)	23 (5.1%)	1 (0.2%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	121	118 (97.5%)	2 (1.7%)	1 (0.8%)	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	59	58 (98.3%)	1 (1.7%)	0	
	TOTAL	629	601 (95.5%)	26 (4.1%)	2 (0.3%)	

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 9/WEEK 24

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL (<30 MSEC)	HIGH (30-60 MSEC)	CONCERN (>60 MSEC)	
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	138	130 (94.2%)	7 (5.1%)	1 (0.7%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	36	36 (100.0%)	0	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	19	18 (94.7%)	1 (5.3%)	0	
	TOTAL	193	184 (95.3%)	8 (4.1%)	1 (0.5%)	
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	306	298 (97.4%)	8 (2.6%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	80	76 (95.0%)	4 (5.0%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	41	40 (97.6%)	1 (2.4%)	0	
	TOTAL	427	414 (97.0%)	13 (3.0%)	0	
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	444	428 (96.4%)	15 (3.4%)	1 (0.2%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	116	112 (96.6%)	4 (3.4%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	60	58 (96.7%)	2 (3.3%)	0	
	TOTAL	620	598 (96.5%)	21 (3.4%)	1 (0.2%)	

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

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TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 10/WEEK 28

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL (<30 MSEC)	HIGH (30-60 MSEC)	CONCERN (>60 MSEC)		
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	135	126 (93.3%)	9 (6.7%)	0		
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	35	33 (94.3%)	2 (5.7%)	0		
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	20	20 (100.0%)	0	0		
	TOTAL	190	179 (94.2%)	11 (5.8%)	0		
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	300	292 (97.3%)	8 (2.7%)	0		
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	81	76 (93.8%)	4 (4.9%)	1 (1.2%)		
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	41	39 (95.1%)	2 (4.9%)	0		
	TOTAL	422	407 (96.4%)	14 (3.3%)	1 (0.2%)		
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	435	418 (96.1%)	17 (3.9%)	0		
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	116	109 (94.0%)	6 (5.2%)	1 (0.9%)		
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	61	59 (96.7%)	2 (3.3%)	0		
	TOTAL	612	586 (95.8%)	25 (4.1%)	1 (0.2%)		

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

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TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 11/WEEK 32

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL (<30 MSEC)	HIGH (30-60 MSEC)	CONCERN (>60 MSEC)	
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	135	128 (94.8%)	6 (4.4%)	1 (0.7%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	33	32 (97.0%)	1 (3.0%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	18	18 (100.0%)	0	0	
	TOTAL	186	178 (95.7%)	7 (3.8%)	1 (0.5%)	
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	299	287 (96.0%)	12 (4.0%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	80	77 (96.3%)	3 (3.8%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	40	39 (97.5%)	1 (2.5%)	0	
	TOTAL	419	403 (96.2%)	16 (3.8%)	0	
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	434	415 (95.6%)	18 (4.1%)	1 (0.2%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	113	109 (96.5%)	4 (3.5%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	58	57 (98.3%)	1 (1.7%)	0	
	TOTAL	605	581 (96.0%)	23 (3.8%)	1 (0.2%)	

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

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TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 12/WEEK 36

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL (<30 MSEC)	HIGH (30-60 MSEC)	CONCERN (>60 MSEC)	
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	135	127 (94.1%)	6 (4.4%)	2 (1.5%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	34	33 (97.1%)	1 (2.9%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	18	18 (100.0%)	0	0	
	TOTAL	187	178 (95.2%)	7 (3.7%)	2 (1.1%)	
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	292	282 (96.6%)	10 (3.4%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	79	77 (97.5%)	2 (2.5%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	39	38 (97.4%)	1 (2.6%)	0	
	TOTAL	410	397 (96.8%)	13 (3.2%)	0	
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	427	409 (95.8%)	16 (3.7%)	2 (0.5%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	113	110 (97.3%)	3 (2.7%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	57	56 (98.2%)	1 (1.8%)	0	
	TOTAL	597	575 (96.3%)	20 (3.4%)	2 (0.3%)	

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

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TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 13/WEEK 40

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL (<30 MSEC)		HIGH (30-60 MSEC)		CONCERN (>60 MSEC)
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	134	128	(95.5%)	6	(4.5%)	0
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	33	32	(97.0%)	1	(3.0%)	0
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	18	17	(94.4%)	0		1 (5.6%)
	TOTAL	185	177	(95.7%)	7	(3.8%)	1 (0.5%)
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	287	279	(97.2%)	8	(2.8%)	0
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	78	75	(96.2%)	3	(3.8%)	0
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	40	38	(95.0%)	2	(5.0%)	0
	TOTAL	405	392	(96.8%)	13	(3.2%)	0
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	421	407	(96.7%)	14	(3.3%)	0
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	111	107	(96.4%)	4	(3.6%)	0
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	58	55	(94.8%)	2	(3.4%)	1 (1.7%)
	TOTAL	590	569	(96.4%)	20	(3.4%)	1 (0.2%)

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

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TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 14/WEEK 44

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL (<30 MSEC)	HIGH (30-60 MSEC)	CONCERN (>60 MSEC)	
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	132	126 (95.5%)	6 (4.5%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	33	33 (100.0%)	0	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	18	18 (100.0%)	0	0	
	TOTAL	183	177 (96.7%)	6 (3.3%)	0	
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	288	276 (95.8%)	12 (4.2%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	77	73 (94.8%)	3 (3.9%)	1 (1.3%)	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	39	39 (100.0%)	0	0	
	TOTAL	404	388 (96.0%)	15 (3.7%)	1 (0.2%)	
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	420	402 (95.7%)	18 (4.3%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	110	106 (96.4%)	3 (2.7%)	1 (0.9%)	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	57	57 (100.0%)	0	0	
	TOTAL	587	565 (96.3%)	21 (3.6%)	1 (0.2%)	

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

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TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 15/WEEK 48

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL (<30 MSEC)	HIGH (30-60 MSEC)	CONCERN (>60 MSEC)	
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	133	124 (93.2%)	9 (6.8%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	33	32 (97.0%)	1 (3.0%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	18	18 (100.0%)	0	0	
	TOTAL	184	174 (94.6%)	10 (5.4%)	0	
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	283	275 (97.2%)	8 (2.8%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	74	69 (93.2%)	5 (6.8%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	39	38 (97.4%)	1 (2.6%)	0	
	TOTAL	396	382 (96.5%)	14 (3.5%)	0	
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	416	399 (95.9%)	17 (4.1%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	107	101 (94.4%)	6 (5.6%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	57	56 (98.2%)	1 (1.8%)	0	
	TOTAL	580	556 (95.9%)	24 (4.1%)	0	

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

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TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 16/WEEK 52

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL (<30 MSEC)	HIGH (30-60 MSEC)	CONCERN (>60 MSEC)	
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	130	123 (94.6%)	7 (5.4%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	33	31 (93.9%)	2 (6.1%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	17	17 (100.0%)	0	0	
	TOTAL	180	171 (95.0%)	9 (5.0%)	0	
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	274	262 (95.6%)	11 (4.0%)	1 (0.4%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	70	68 (97.1%)	2 (2.9%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	39	38 (97.4%)	1 (2.6%)	0	
	TOTAL	383	368 (96.1%)	14 (3.7%)	1 (0.3%)	
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	404	385 (95.3%)	18 (4.5%)	1 (0.2%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	103	99 (96.1%)	4 (3.9%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	56	55 (98.2%)	1 (1.8%)	0	
	TOTAL	563	539 (95.7%)	23 (4.1%)	1 (0.2%)	

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 17/WEEK 56

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL (<30 MSEC)	HIGH (30-60 MSEC)	CONCERN (>60 MSEC)	
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	121	112 (92.6%)	9 (7.4%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	33	31 (93.9%)	2 (6.1%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	15	15 (100.0%)	0	0	
	TOTAL	169	158 (93.5%)	11 (6.5%)	0	
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	259	246 (95.0%)	10 (3.9%)	3 (1.2%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	68	65 (95.6%)	3 (4.4%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	37	36 (97.3%)	1 (2.7%)	0	
	TOTAL	364	347 (95.3%)	14 (3.8%)	3 (0.8%)	
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	380	358 (94.2%)	19 (5.0%)	3 (0.8%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	101	96 (95.0%)	5 (5.0%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	52	51 (98.1%)	1 (1.9%)	0	
	TOTAL	533	505 (94.7%)	25 (4.7%)	3 (0.6%)	

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 18/WEEK 60

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL (<30 MSEC)		HIGH (30-60 MSEC)		CONCERN (>60 MSEC)
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	124	113	(91.1%)	11	(8.9%)	0
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	32	30	(93.8%)	2	(6.3%)	0
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	17	16	(94.1%)	1	(5.9%)	0
	TOTAL	173	159	(91.9%)	14	(8.1%)	0
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	265	251	(94.7%)	12	(4.5%)	2 (0.8%)
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	70	66	(94.3%)	3	(4.3%)	1 (1.4%)
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	38	38	(100.0%)	0		0
	TOTAL	373	355	(95.2%)	15	(4.0%)	3 (0.8%)
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	389	364	(93.6%)	23	(5.9%)	2 (0.5%)
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	102	96	(94.1%)	5	(4.9%)	1 (1.0%)
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	55	54	(98.2%)	1	(1.8%)	0
	TOTAL	546	514	(94.1%)	29	(5.3%)	3 (0.5%)

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

SB 207499

TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 19/WEEK 64

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL (<30 MSEC)		HIGH (30-60 MSEC)		CONCERN (>60 MSEC)	
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	104	99	(95.2%)	4	(3.8%)	1	(1.0%)
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	25	24	(96.0%)	0		1	(4.0%)
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	13	13	(100.0%)	0		0	
	TOTAL	142	136	(95.8%)	4	(2.8%)	2	(1.4%)
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	219	204	(93.2%)	14	(6.4%)	1	(0.5%)
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	58	57	(98.3%)	1	(1.7%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	31	30	(96.8%)	1	(3.2%)	0	
	TOTAL	308	291	(94.5%)	16	(5.2%)	1	(0.3%)
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	323	303	(93.8%)	18	(5.6%)	2	(0.6%)
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	83	81	(97.6%)	1	(1.2%)	1	(1.2%)
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	44	43	(97.7%)	1	(2.3%)	0	
	TOTAL	450	427	(94.9%)	20	(4.4%)	3	(0.7%)

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

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TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 20/WEEK 68

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL (<30 MSEC)	HIGH (30-60 MSEC)	CONCERN (>60 MSEC)	
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	102	97 (95.1%)	5 (4.9%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	25	25 (100.0%)	0	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	13	13 (100.0%)	0	0	
	TOTAL	140	135 (96.4%)	5 (3.6%)	0	
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	209	195 (93.3%)	14 (6.7%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	57	55 (96.5%)	2 (3.5%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	29	29 (100.0%)	0	0	
	TOTAL	295	279 (94.6%)	16 (5.4%)	0	
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	311	292 (93.9%)	19 (6.1%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	82	80 (97.6%)	2 (2.4%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	42	42 (100.0%)	0	0	
	TOTAL	435	414 (95.2%)	21 (4.8%)	0	

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

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TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 21/WEEK 72

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL (<30 MSEC)	HIGH (30-60 MSEC)	CONCERN (>60 MSEC)	
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	122	115 (94.3%)	6 (4.9%)	1 (0.8%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	31	30 (96.8%)	1 (3.2%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	17	17 (100.0%)	0	0	
	TOTAL	170	162 (95.3%)	7 (4.1%)	1 (0.6%)	
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	254	243 (95.7%)	11 (4.3%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	66	66 (100.0%)	0	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	37	36 (97.3%)	0	1 (2.7%)	
	TOTAL	357	345 (96.6%)	11 (3.1%)	1 (0.3%)	
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	376	358 (95.2%)	17 (4.5%)	1 (0.3%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	97	96 (99.0%)	1 (1.0%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	54	53 (98.1%)	0	1 (1.9%)	
	TOTAL	527	507 (96.2%)	18 (3.4%)	2 (0.4%)	

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

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TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 22/WEEK 76

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL (<30 MSEC)	HIGH (30-60 MSEC)	CONCERN (>60 MSEC)	
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	73	68 (93.2%)	5 (6.8%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	18	16 (88.9%)	2 (11.1%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	9	9 (100.0%)	0	0	
	TOTAL	100	93 (93.0%)	7 (7.0%)	0	
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	148	144 (97.3%)	3 (2.0%)	1 (0.7%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	37	36 (97.3%)	1 (2.7%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	13	13 (100.0%)	0	0	
	TOTAL	198	193 (97.5%)	4 (2.0%)	1 (0.5%)	
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	221	212 (95.9%)	8 (3.6%)	1 (0.5%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	55	52 (94.5%)	3 (5.5%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	22	22 (100.0%)	0	0	
	TOTAL	298	286 (96.0%)	11 (3.7%)	1 (0.3%)	

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

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TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 23/WEEK 80

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL (<30 MSEC)	HIGH (30-60 MSEC)	CONCERN (>60 MSEC)	
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	72	69 (95.8%)	3 (4.2%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	17	17 (100.0%)	0	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	9	8 (88.9%)	1 (11.1%)	0	
	TOTAL	98	94 (95.9%)	4 (4.1%)	0	
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	147	138 (93.9%)	4 (2.7%)	5 (3.4%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	34	33 (97.1%)	1 (2.9%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	12	12 (100.0%)	0	0	
	TOTAL	193	183 (94.8%)	5 (2.6%)	5 (2.6%)	
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	219	207 (94.5%)	7 (3.2%)	5 (2.3%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	51	50 (98.0%)	1 (2.0%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	21	20 (95.2%)	1 (4.8%)	0	
	TOTAL	291	277 (95.2%)	9 (3.1%)	5 (1.7%)	

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 24/WEEK 84

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL (<30 MSEC)	HIGH (30-60 MSEC)	CONCERN (>60 MSEC)	
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	118	109 (92.4%)	7 (5.9%)	2 (1.7%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	30	29 (96.7%)	1 (3.3%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	15	14 (93.3%)	1 (6.7%)	0	
	TOTAL	163	152 (93.3%)	9 (5.5%)	2 (1.2%)	
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	240	230 (95.8%)	10 (4.2%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	59	57 (96.6%)	2 (3.4%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	35	34 (97.1%)	1 (2.9%)	0	
	TOTAL	334	321 (96.1%)	13 (3.9%)	0	
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	358	339 (94.7%)	17 (4.7%)	2 (0.6%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	89	86 (96.6%)	3 (3.4%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	50	48 (96.0%)	2 (4.0%)	0	
	TOTAL	497	473 (95.2%)	22 (4.4%)	2 (0.4%)	

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

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TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 25/WEEK 88

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL (<30 MSEC)	HIGH (30-60 MSEC)	CONCERN (>60 MSEC)	
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	43	41 (95.3%)	2 (4.7%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	7	7 (100.0%)	0	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	3	3 (100.0%)	0	0	
	TOTAL	53	51 (96.2%)	2 (3.8%)	0	
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	76	71 (93.4%)	5 (6.6%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	17	17 (100.0%)	0	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	4	4 (100.0%)	0	0	
	TOTAL	97	92 (94.8%)	5 (5.2%)	0	
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	119	112 (94.1%)	7 (5.9%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	24	24 (100.0%)	0	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	7	7 (100.0%)	0	0	
	TOTAL	150	143 (95.3%)	7 (4.7%)	0	

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

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TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 26/WEEK 92

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL (<30 MSEC)	HIGH (30-60 MSEC)	CONCERN (>60 MSEC)	
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	42	37 (88.1%)	5 (11.9%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	7	6 (85.7%)	1 (14.3%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	3	3 (100.0%)	0	0	
	TOTAL	52	46 (88.5%)	6 (11.5%)	0	
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	75	72 (96.0%)	3 (4.0%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	17	16 (94.1%)	1 (5.9%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	4	4 (100.0%)	0	0	
	TOTAL	96	92 (95.8%)	4 (4.2%)	0	
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	117	109 (93.2%)	8 (6.8%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	24	22 (91.7%)	2 (8.3%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	7	7 (100.0%)	0	0	
	TOTAL	148	138 (93.2%)	10 (6.8%)	0	

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

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TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 27/WEEK 96

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL (<30 MSEC)	HIGH (30-60 MSEC)	CONCERN (>60 MSEC)	
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	114	105 (92.1%)	8 (7.0%)	1 (0.9%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	30	29 (96.7%)	1 (3.3%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	16	16 (100.0%)	0	0	
	TOTAL	160	150 (93.8%)	9 (5.6%)	1 (0.6%)	
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	233	219 (94.0%)	12 (5.2%)	2 (0.9%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	59	57 (96.6%)	2 (3.4%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	36	35 (97.2%)	1 (2.8%)	0	
	TOTAL	328	311 (94.8%)	15 (4.6%)	2 (0.6%)	
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	347	324 (93.4%)	20 (5.8%)	3 (0.9%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	89	86 (96.6%)	3 (3.4%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	52	51 (98.1%)	1 (1.9%)	0	
	TOTAL	488	461 (94.5%)	24 (4.9%)	3 (0.6%)	

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

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TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 28/WEEK 100

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----		
			NORMAL (<30 MSEC)	HIGH (30-60 MSEC)	CONCERN (>60 MSEC)
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	19	19 (100.0%)	0	0
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	2	2 (100.0%)	0	0
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	1	1 (100.0%)	0	0
	TOTAL	22	22 (100.0%)	0	0
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	38	35 (92.1%)	3 (7.9%)	0
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	10	10 (100.0%)	0	0
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	1	1 (100.0%)	0	0
	TOTAL	49	46 (93.9%)	3 (6.1%)	0
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	57	54 (94.7%)	3 (5.3%)	0
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	12	12 (100.0%)	0	0
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	2	2 (100.0%)	0	0
	TOTAL	71	68 (95.8%)	3 (4.2%)	0

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

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TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 29/WEEK 104

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL (<30 MSEC)	HIGH (30-60 MSEC)	CONCERN (>60 MSEC)	
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	16	15 (93.8%)	1 (6.3%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	2	2 (100.0%)	0	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0	0	0	
	TOTAL	18	17 (94.4%)	1 (5.6%)	0	
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	29	26 (89.7%)	2 (6.9%)	1 (3.4%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	10	10 (100.0%)	0	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0	0	0	
	TOTAL	39	36 (92.3%)	2 (5.1%)	1 (2.6%)	
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	45	41 (91.1%)	3 (6.7%)	1 (2.2%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	12	12 (100.0%)	0	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0	0	0	
	TOTAL	57	53 (93.0%)	3 (5.3%)	1 (1.8%)	

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

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TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 30/WEEK 108

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL (<30 MSEC)	HIGH (30-60 MSEC)	CONCERN (>60 MSEC)	
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	88	79 (89.8%)	9 (10.2%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	25	25 (100.0%)	0	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	13	13 (100.0%)	0	0	
	TOTAL	126	117 (92.9%)	9 (7.1%)	0	
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	191	183 (95.8%)	7 (3.7%)	1 (0.5%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	48	47 (97.9%)	1 (2.1%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	33	32 (97.0%)	0	1 (3.0%)	
	TOTAL	272	262 (96.3%)	8 (2.9%)	2 (0.7%)	
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	279	262 (93.9%)	16 (5.7%)	1 (0.4%)	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	73	72 (98.6%)	1 (1.4%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	46	45 (97.8%)	0	1 (2.2%)	
	TOTAL	398	379 (95.2%)	17 (4.3%)	2 (0.5%)	

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

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TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 31/WEEK 112

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----		
			NORMAL (<30 MSEC)	HIGH (30-60 MSEC)	CONCERN (>60 MSEC)
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	8	8 (100.0%)	0	0
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	1	1 (100.0%)	0	0
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0	0	0
	TOTAL	9	9 (100.0%)	0	0
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	10	9 (90.0%)	1 (10.0%)	0
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	8	8 (100.0%)	0	0
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0	0	0
	TOTAL	18	17 (94.4%)	1 (5.6%)	0
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	18	17 (94.4%)	1 (5.6%)	0
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	9	9 (100.0%)	0	0
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0	0	0
	TOTAL	27	26 (96.3%)	1 (3.7%)	0

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

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TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 32/WEEK 116

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL (<30 MSEC)	HIGH (30-60 MSEC)	CONCERN (>60 MSEC)	
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	8	6 (75.0%)	2 (25.0%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	1	1 (100.0%)	0	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0	0	0	
	TOTAL	9	7 (77.8%)	2 (22.2%)	0	
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	8	8 (100.0%)	0	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	7	7 (100.0%)	0	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0	0	0	
	TOTAL	15	15 (100.0%)	0	0	
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	16	14 (87.5%)	2 (12.5%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	8	8 (100.0%)	0	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0	0	0	
	TOTAL	24	22 (91.7%)	2 (8.3%)	0	

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

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TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 33/WEEK 120

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL (<30 MSEC)	HIGH (30-60 MSEC)	CONCERN (>60 MSEC)	
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	66	63 (95.5%)	3 (4.5%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	16	15 (93.8%)	1 (6.3%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	9	9 (100.0%)	0	0	
	TOTAL	91	87 (95.6%)	4 (4.4%)	0	
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	132	129 (97.7%)	3 (2.3%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	34	33 (97.1%)	1 (2.9%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	21	19 (90.5%)	2 (9.5%)	0	
	TOTAL	187	181 (96.8%)	6 (3.2%)	0	
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	198	192 (97.0%)	6 (3.0%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	50	48 (96.0%)	2 (4.0%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	30	28 (93.3%)	2 (6.7%)	0	
	TOTAL	278	268 (96.4%)	10 (3.6%)	0	

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

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TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 34/WEEK 124

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----		
			NORMAL (<30 MSEC)	HIGH (30-60 MSEC)	CONCERN (>60 MSEC)
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	3	3 (100.0%)	0	0
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	0	0	0	0
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0	0	0
	TOTAL	3	3 (100.0%)	0	0
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	2	2 (100.0%)	0	0
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	1	0	1 (100.0%)	0
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0	0	0
	TOTAL	3	2 (66.7%)	1 (33.3%)	0
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	5	5 (100.0%)	0	0
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	1	0	1 (100.0%)	0
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0	0	0
	TOTAL	6	5 (83.3%)	1 (16.7%)	0

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

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TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 35/WEEK 128

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL (<30 MSEC)	HIGH (30-60 MSEC)	CONCERN (>60 MSEC)	
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	3	2 (66.7%)	1 (33.3%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	0	0	0	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0	0	0	
	TOTAL	3	2 (66.7%)	1 (33.3%)	0	
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	2	2 (100.0%)	0	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	1	1 (100.0%)	0	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0	0	0	
	TOTAL	3	3 (100.0%)	0	0	
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	5	4 (80.0%)	1 (20.0%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	1	1 (100.0%)	0	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0	0	0	
	TOTAL	6	5 (83.3%)	1 (16.7%)	0	

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

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TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 36/WEEK 132

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----			
			NORMAL (<30 MSEC)	HIGH (30-60 MSEC)	CONCERN (>60 MSEC)	
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	28	26 (92.9%)	2 (7.1%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	5	5 (100.0%)	0	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	3	3 (100.0%)	0	0	
	TOTAL	36	34 (94.4%)	2 (5.6%)	0	
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	40	39 (97.5%)	1 (2.5%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	16	15 (93.8%)	1 (6.3%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	2	1 (50.0%)	1 (50.0%)	0	
	TOTAL	58	55 (94.8%)	3 (5.2%)	0	
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	68	65 (95.6%)	3 (4.4%)	0	
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	21	20 (95.2%)	1 (4.8%)	0	
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	5	4 (80.0%)	1 (20.0%)	0	
	TOTAL	94	89 (94.7%)	5 (5.3%)	0	

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

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TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: VISIT 37/WEEK 136

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----		
			NORMAL (<30 MSEC)	HIGH (30-60 MSEC)	CONCERN (>60 MSEC)
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	1	1 (100.0%)	0	0
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	0	0	0	0
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0	0	0
	TOTAL	1	1 (100.0%)	0	0
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	2	2 (100.0%)	0	0
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	0	0	0	0
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0	0	0
	TOTAL	2	2 (100.0%)	0	0
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	3	3 (100.0%)	0	0
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	0	0	0	0
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	0	0	0	0
	TOTAL	3	3 (100.0%)	0	0

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

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TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PRIOR TREATMENT	PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----					
			NORMAL (<30 MSEC)		HIGH (30-60 MSEC)		CONCERN (>60 MSEC)	
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	174	113	(64.9%)	53	(30.5%)	8	(4.6%)
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	40	27	(67.5%)	12	(30.0%)	1	(2.5%)
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	25	21	(84.0%)	3	(12.0%)	1	(4.0%)
	TOTAL	239	161	(67.4%)	68	(28.5%)	10	(4.2%)
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	334	225	(67.4%)	90	(26.9%)	19	(5.7%)
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	93	62	(66.7%)	28	(30.1%)	3	(3.2%)
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	44	37	(84.1%)	5	(11.4%)	2	(4.5%)
	TOTAL	471	324	(68.8%)	123	(26.1%)	24	(5.1%)
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	508	338	(66.5%)	143	(28.1%)	27	(5.3%)
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	133	89	(66.9%)	40	(30.1%)	4	(3.0%)
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	69	58	(84.1%)	8	(11.6%)	3	(4.3%)
	TOTAL	710	485	(68.3%)	191	(26.9%)	34	(4.8%)

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

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TABLE 15.19B

CHANGE FROM BASELINE IN QTC BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

PARAMETER: QTC INTERVAL-CHANGE FROM BASELINE TIME POINT: ENDPOINT

PRIOR TREATMENT	BASELINE	NUMBER OF PATIENTS TESTED	-----ON-THERAPY-----				
			NORMAL (<30 MSEC)		HIGH (30-60 MSEC)		CONCERN (>60 MSEC)
PLACEBO	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	174	163	(93.7%)	11	(6.3%)	0
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	40	38	(95.0%)	2	(5.0%)	0
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	25	25	(100.0%)	0		0
	TOTAL	239	226	(94.6%)	13	(5.4%)	0
SB 207499	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	334	314	(94.0%)	19	(5.7%)	1 (0.3%)
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	93	88	(94.6%)	5	(5.4%)	0
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	44	41	(93.2%)	2	(4.5%)	1 (2.3%)
	TOTAL	471	443	(94.1%)	26	(5.5%)	2 (0.4%)
TOTAL	NORMAL (<430 MSEC [MALE] AND <450 MSEC [FEMALE])	508	477	(93.9%)	30	(5.9%)	1 (0.2%)
	HIGH (430-450 MSEC [MALE] AND 450-470 MSEC [FEMALE])	133	126	(94.7%)	7	(5.3%)	0
	CONCERN (>450 MSEC [MALE] AND >470 MSEC [FEMALE])	69	66	(95.7%)	2	(2.9%)	1 (1.4%)
	TOTAL	710	669	(94.2%)	39	(5.5%)	2 (0.3%)

1. PATIENTS ARE ASSIGNED TO CATEGORY BASED ON THEIR HIGHEST ON-THERAPY CHANGE
2. PERCENTAGES ARE BASED ON THE NUMBER OF PATIENTS TESTED WITHIN EACH BASELINE CATEGORY
3. ENDPOINT=LAST VALUE REPORTED ON-THERAPY
4. ON-THERAPY IS DEFINED AS ECGS COLLECTED DURING EXTENSION PERIOD

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TABLE 15.20

INCIDENCE OF NEW-ONSET ECG ABNORMALITIES BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

ECG ABNORMALITY		PLACEBO (N= 243)	PRIOR TREATMENT SB 207499 (N= 480)	TOTAL (N= 723)
ARRHYTHMIA ATRIAL NOS	NOT PRESENT AT BASELINE OR SCREENING NEW ONSET	243 1 (0.4%)	480 0 .	723 1 (0.1%)
ARRHYTHMIA SINUS NODE NOS	NOT PRESENT AT BASELINE OR SCREENING NEW ONSET	243 1 (0.4%)	480 3 (0.6%)	723 4 (0.6%)
ATRIAL FIBRILLATION	NOT PRESENT AT BASELINE OR SCREENING NEW ONSET	235 6 (2.6%)	470 16 (3.4%)	705 22 (3.1%)
ATRIAL FLUTTER	NOT PRESENT AT BASELINE OR SCREENING NEW ONSET	242 2 (0.8%)	478 4 (0.8%)	720 6 (0.8%)
ATRIAL HYPERTROPHY NOS	NOT PRESENT AT BASELINE OR SCREENING NEW ONSET	227 51 (22.5%)	457 85 (18.6%)	684 136 (19.9%)
ATRIAL TACHYCARDIA NOS	NOT PRESENT AT BASELINE OR SCREENING NEW ONSET	243 1 (0.4%)	480 1 (0.2%)	723 2 (0.3%)
AV JUNCTIONAL RHYTHM	NOT PRESENT AT BASELINE OR SCREENING NEW ONSET	242 1 (0.4%)	480 1 (0.2%)	722 2 (0.3%)
AXIS NOT AVAILABLE	NOT PRESENT AT BASELINE OR SCREENING NEW ONSET	243 0 .	480 1 (0.2%)	723 1 (0.1%)
BIFASCICULAR BLOCK	NOT PRESENT AT BASELINE OR SCREENING NEW ONSET	240 4 (1.7%)	476 5 (1.1%)	716 9 (1.3%)
BIGEMINY	NOT PRESENT AT BASELINE OR SCREENING NEW ONSET	243 1 (0.4%)	480 3 (0.6%)	723 4 (0.6%)
BRADYCARDIA NOS	NOT PRESENT AT BASELINE OR SCREENING NEW ONSET	237 8 (3.4%)	469 21 (4.5%)	706 29 (4.1%)
CARDIAC RATE NOS	NOT PRESENT AT BASELINE OR SCREENING NEW ONSET	242 3 (1.2%)	479 0 .	721 3 (0.4%)
CARDIAC RHYTHM ABNORMAL NOS	NOT PRESENT AT BASELINE OR SCREENING NEW ONSET	243 4 (1.6%)	479 2 (0.4%)	722 6 (0.8%)
CARDIAC RHYTHM NOS	NOT PRESENT AT BASELINE OR SCREENING	242	479	721

1. EACH DISTINCT PATIENT COUNTED ONCE PER ABNORMALITY

2. PERCENTAGES FOR EACH ABNORMALITY ARE BASED ON NUMBER OF PATIENTS WITH SPECIFIC ABNORMALITY ABSENT AT BASELINE AND SCREENING

TABLE 15.20

INCIDENCE OF NEW-ONSET ECG ABNORMALITIES BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

ECG ABNORMALITY		PLACEBO (N= 243)	PRIOR TREATMENT SB 207499 (N= 480)	TOTAL (N= 723)
CARDIAC RHYTHM NOS	NEW ONSET	1 (0.4%)	2 (0.4%)	3 (0.4%)
DECREASED VOLTAGE EKG	NOT PRESENT AT BASELINE OR SCREENING	238	470	708
	NEW ONSET	9 (3.8%)	15 (3.2%)	24 (3.4%)
DIGITALIS EFFECT EKG (E-)	NOT PRESENT AT BASELINE OR SCREENING	243	479	722
	NEW ONSET	1 (0.4%)	0	1 (0.1%)
ECTOPIC ATRIAL BEATS NOS	NOT PRESENT AT BASELINE OR SCREENING	239	474	713
	NEW ONSET	28 (11.7%)	45 (9.5%)	73 (10.2%)
ECTOPIC RHYTHM NOS	NOT PRESENT AT BASELINE OR SCREENING	243	477	720
	NEW ONSET	1 (0.4%)	12 (2.5%)	13 (1.8%)
FIRST DEGREE AV BLOCK	NOT PRESENT AT BASELINE OR SCREENING	235	454	689
	NEW ONSET	15 (6.4%)	27 (5.9%)	42 (6.1%)
FLUTTER-FIBRILLATION	NOT PRESENT AT BASELINE OR SCREENING	243	479	722
	NEW ONSET	0	1 (0.2%)	1 (0.1%)
HEART BLOCK NOS	NOT PRESENT AT BASELINE OR SCREENING	243	480	723
	NEW ONSET	1 (0.4%)	0	1 (0.1%)
INCOMPLETE BUNDLE BRANCH BLOCK	NOT PRESENT AT BASELINE OR SCREENING	229	451	680
	NEW ONSET	31 (13.5%)	54 (12.0%)	85 (12.5%)
INDETERMINATE AXIS EKG	NOT PRESENT AT BASELINE OR SCREENING	243	478	721
	NEW ONSET	19 (7.8%)	41 (8.6%)	60 (8.3%)
INTRAVENTRICULAR BLOCK NOS	NOT PRESENT AT BASELINE OR SCREENING	217	454	671
	NEW ONSET	44 (20.3%)	91 (20.0%)	135 (20.1%)
JUNCTIONAL ESCAPE BEATS	NOT PRESENT AT BASELINE OR SCREENING	243	480	723
	NEW ONSET	0	1 (0.2%)	1 (0.1%)
LEFT ANTERIOR HEMIBLOCK	NOT PRESENT AT BASELINE OR SCREENING	227	443	670
	NEW ONSET	20 (8.8%)	30 (6.8%)	50 (7.5%)
LEFT ATRIAL HYPERTROPHY (P MITRALE)	NOT PRESENT AT BASELINE OR SCREENING	220	444	664
	NEW ONSET	19 (8.6%)	36 (8.1%)	55 (8.3%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER ABNORMALITY

2. PERCENTAGES FOR EACH ABNORMALITY ARE BASED ON NUMBER OF PATIENTS WITH SPECIFIC ABNORMALITY ABSENT AT BASELINE AND SCREENING

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TABLE 15.20

INCIDENCE OF NEW-ONSET ECG ABNORMALITIES BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

ECG ABNORMALITY		PLACEBO (N= 243)	PRIOR TREATMENT SB 207499 (N= 480)	TOTAL (N= 723)
LEFT AXIS DEVIATION EKG	NOT PRESENT AT BASELINE OR SCREENING NEW ONSET	233 21 (9.0%)	462 41 (8.9%)	695 62 (8.9%)
LEFT BUNDLE BRANCH BLOCK NOS	NOT PRESENT AT BASELINE OR SCREENING NEW ONSET	241 0 .	476 7 (1.5%)	717 7 (1.0%)
LEFT POSTERIOR HEMIBLOCK	NOT PRESENT AT BASELINE OR SCREENING NEW ONSET	243 1 (0.4%)	478 5 (1.0%)	721 6 (0.8%)
LEFT VENTRICULAR HYPERTROPHY	NOT PRESENT AT BASELINE OR SCREENING NEW ONSET	233 17 (7.3%)	473 32 (6.8%)	706 49 (6.9%)
LOW VENTRICULAR VOLTAGE NOS	NOT PRESENT AT BASELINE OR SCREENING NEW ONSET	241 12 (5.0%)	475 40 (8.4%)	716 52 (7.3%)
MYOCARDIAL INFARCTION ANTERIOR OLD	NOT PRESENT AT BASELINE OR SCREENING NEW ONSET	241 1 (0.4%)	473 3 (0.6%)	714 4 (0.6%)
MYOCARDIAL INFARCTION INFERIOR ACUTE	NOT PRESENT AT BASELINE OR SCREENING NEW ONSET	243 1 (0.4%)	479 0 .	722 1 (0.1%)
MYOCARDIAL INFARCTION INFERIOR OLD	NOT PRESENT AT BASELINE OR SCREENING NEW ONSET	224 11 (4.9%)	456 30 (6.6%)	680 41 (6.0%)
MYOCARDIAL INFARCTION LATERAL OLD	NOT PRESENT AT BASELINE OR SCREENING NEW ONSET	243 4 (1.6%)	473 12 (2.5%)	716 16 (2.2%)
MYOCARDIAL INFARCTION POSTERIOR OLD	NOT PRESENT AT BASELINE OR SCREENING NEW ONSET	242 0 .	480 1 (0.2%)	722 1 (0.1%)
MYOCARDIAL INFARCTION SEPTAL OLD	NOT PRESENT AT BASELINE OR SCREENING NEW ONSET	222 29 (13.1%)	434 52 (12.0%)	656 81 (12.3%)
MYOCARDIAL ISCHEMIA ANTERIOR	NOT PRESENT AT BASELINE OR SCREENING NEW ONSET	243 4 (1.6%)	479 5 (1.0%)	722 9 (1.2%)
MYOCARDIAL ISCHEMIA INFERIOR	NOT PRESENT AT BASELINE OR SCREENING NEW ONSET	241 3 (1.2%)	478 4 (0.8%)	719 7 (1.0%)
MYOCARDIAL ISCHEMIA LATERAL	NOT PRESENT AT BASELINE OR SCREENING	240	477	717

1. EACH DISTINCT PATIENT COUNTED ONCE PER ABNORMALITY

2. PERCENTAGES FOR EACH ABNORMALITY ARE BASED ON NUMBER OF PATIENTS WITH SPECIFIC ABNORMALITY ABSENT AT BASELINE AND SCREENING

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TABLE 15.20

INCIDENCE OF NEW-ONSET ECG ABNORMALITIES BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

ECG ABNORMALITY		PLACEBO (N= 243)	PRIOR TREATMENT SB 207499 (N= 480)	TOTAL (N= 723)
MYOCARDIAL ISCHEMIA LATERAL	NEW ONSET	4 (1.7%)	8 (1.7%)	12 (1.7%)
MYOCARDIAL ISCHEMIA SEPTAL	NOT PRESENT AT BASELINE OR SCREENING	243	480	723
	NEW ONSET	3 (1.2%)	4 (0.8%)	7 (1.0%)
P AXIS NOT AVAILABLE	NOT PRESENT AT BASELINE OR SCREENING	243	480	723
	NEW ONSET	1 (0.4%)	0	1 (0.1%)
PACEMAKER ABNORMAL RATE	NOT PRESENT AT BASELINE OR SCREENING	243	480	723
	NEW ONSET	1 (0.4%)	1 (0.2%)	2 (0.3%)
PACEMAKER NORMAL FUNCTION	NOT PRESENT AT BASELINE OR SCREENING	242	479	721
	NEW ONSET	1 (0.4%)	2 (0.4%)	3 (0.4%)
POOR R-WAVE PROGRESSION	NOT PRESENT AT BASELINE OR SCREENING	232	460	692
	NEW ONSET	41 (17.7%)	84 (18.3%)	125 (18.1%)
PRE-EXCITATION SYNDROME NOS	NOT PRESENT AT BASELINE OR SCREENING	241	477	718
	NEW ONSET	6 (2.5%)	5 (1.0%)	11 (1.5%)
PREMATURE ATRIAL CONTRACTIONS NOS	NOT PRESENT AT BASELINE OR SCREENING	233	467	700
	NEW ONSET	47 (20.2%)	88 (18.8%)	135 (19.3%)
PREMATURE VENTRICULAR CONTRACTIONS NOS	NOT PRESENT AT BASELINE OR SCREENING	232	453	685
	NEW ONSET	48 (20.7%)	117 (25.8%)	165 (24.1%)
Q-T INTERVAL INCREASED	NOT PRESENT AT BASELINE OR SCREENING	203	419	622
	NEW ONSET	54 (26.6%)	131 (31.3%)	185 (29.7%)
RIGHT ATRIAL HYPERTROPHY (P PULMONALE)	NOT PRESENT AT BASELINE OR SCREENING	240	475	715
	NEW ONSET	8 (3.3%)	14 (2.9%)	22 (3.1%)
RIGHT AXIS DEVIATION EKG	NOT PRESENT AT BASELINE OR SCREENING	228	462	690
	NEW ONSET	15 (6.6%)	43 (9.3%)	58 (8.4%)
RIGHT BUNDLE BRANCH BLOCK	NOT PRESENT AT BASELINE OR SCREENING	228	452	680
	NEW ONSET	7 (3.1%)	20 (4.4%)	27 (4.0%)
RIGHT VENTRICULAR HYPERTROPHY	NOT PRESENT AT BASELINE OR SCREENING	241	476	717
	NEW ONSET	2 (0.8%)	8 (1.7%)	10 (1.4%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER ABNORMALITY

2. PERCENTAGES FOR EACH ABNORMALITY ARE BASED ON NUMBER OF PATIENTS WITH SPECIFIC ABNORMALITY ABSENT AT BASELINE AND SCREENING

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TABLE 15.20

INCIDENCE OF NEW-ONSET ECG ABNORMALITIES BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

ECG ABNORMALITY		PLACEBO (N= 243)	PRIOR TREATMENT SB 207499 (N= 480)	TOTAL (N= 723)
S-T CHANGES NONSPECIFIC	NOT PRESENT AT BASELINE OR SCREENING	205	420	625
	NEW ONSET	44 (21.5%)	70 (16.7%)	114 (18.2%)
S-T CHANGES NOS	NOT PRESENT AT BASELINE OR SCREENING	243	479	722
	NEW ONSET	1 (0.4%)	0 .	1 (0.1%)
S-T CHANGES PERICARDIAL	NOT PRESENT AT BASELINE OR SCREENING	242	479	721
	NEW ONSET	0 .	1 (0.2%)	1 (0.1%)
S-T CHANGES SEGMENT ELEVATION	NOT PRESENT AT BASELINE OR SCREENING	242	479	721
	NEW ONSET	4 (1.7%)	4 (0.8%)	8 (1.1%)
S-T CHANGES STRAIN	NOT PRESENT AT BASELINE OR SCREENING	242	477	719
	NEW ONSET	1 (0.4%)	1 (0.2%)	2 (0.3%)
S-T CHANGES SUBENDOCARDIAL	NOT PRESENT AT BASELINE OR SCREENING	243	480	723
	NEW ONSET	2 (0.8%)	1 (0.2%)	3 (0.4%)
S-T SEGMENT DEPRESSION	NOT PRESENT AT BASELINE OR SCREENING	243	479	722
	NEW ONSET	2 (0.8%)	0 .	2 (0.3%)
SECOND DEGREE AV BLOCK MOBILZ TYPE I	NOT PRESENT AT BASELINE OR SCREENING	243	480	723
	NEW ONSET	0 .	1 (0.2%)	1 (0.1%)
SECOND DEGREE AV BLOCK MOBILZ TYPE II	NOT PRESENT AT BASELINE OR SCREENING	243	480	723
	NEW ONSET	0 .	1 (0.2%)	1 (0.1%)
SICK SINUS SYNDROME	NOT PRESENT AT BASELINE OR SCREENING	243	480	723
	NEW ONSET	1 (0.4%)	0 .	1 (0.1%)
SINUS ARRHYTHMIA	NOT PRESENT AT BASELINE OR SCREENING	242	480	722
	NEW ONSET	3 (1.2%)	1 (0.2%)	4 (0.6%)
SINUS BRADYCARDIA	NOT PRESENT AT BASELINE OR SCREENING	208	406	614
	NEW ONSET	41 (19.7%)	94 (23.2%)	135 (22.0%)
SINUS TACHYCARDIA	NOT PRESENT AT BASELINE OR SCREENING	233	460	693
	NEW ONSET	45 (19.3%)	73 (15.9%)	118 (17.0%)
T WAVE ABNORMAL,NOS	NOT PRESENT AT BASELINE OR SCREENING	231	470	701

1. EACH DISTINCT PATIENT COUNTED ONCE PER ABNORMALITY

2. PERCENTAGES FOR EACH ABNORMALITY ARE BASED ON NUMBER OF PATIENTS WITH SPECIFIC ABNORMALITY ABSENT AT BASELINE AND SCREENING

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TABLE 15.20

INCIDENCE OF NEW-ONSET ECG ABNORMALITIES BY PRIOR TREATMENT IN STUDIES 042/091

PROTOCOL 040

ECG ABNORMALITY		PLACEBO (N= 243)	PRIOR TREATMENT SB 207499 (N= 480)	TOTAL (N= 723)
T WAVE ABNORMAL,NOS	NEW ONSET	38 (16.5%)	65 (13.8%)	103 (14.7%)
T-WAVE FLAT	NOT PRESENT AT BASELINE OR SCREENING	243	479	722
	NEW ONSET	1 (0.4%)	1 (0.2%)	2 (0.3%)
T-WAVE INVERSION	NOT PRESENT AT BASELINE OR SCREENING	243	478	721
	NEW ONSET	2 (0.8%)	2 (0.4%)	4 (0.6%)
T-WAVE PEAKED	NOT PRESENT AT BASELINE OR SCREENING	241	480	721
	NEW ONSET	2 (0.8%)	2 (0.4%)	4 (0.6%)
TACHYCARDIA NOS	NOT PRESENT AT BASELINE OR SCREENING	241	477	718
	NEW ONSET	8 (3.3%)	18 (3.8%)	26 (3.6%)
U WAVE	NOT PRESENT AT BASELINE OR SCREENING	243	480	723
	NEW ONSET	1 (0.4%)	2 (0.4%)	3 (0.4%)
VENTRICULAR COUPLETS	NOT PRESENT AT BASELINE OR SCREENING	243	480	723
	NEW ONSET	2 (0.8%)	3 (0.6%)	5 (0.7%)
VENTRICULAR HYPERTROPHY NOS	NOT PRESENT AT BASELINE OR SCREENING	239	463	702
	NEW ONSET	10 (4.2%)	15 (3.2%)	25 (3.6%)

1. EACH DISTINCT PATIENT COUNTED ONCE PER ABNORMALITY

2. PERCENTAGES FOR EACH ABNORMALITY ARE BASED ON NUMBER OF PATIENTS WITH SPECIFIC ABNORMALITY ABSENT AT BASELINE AND SCREENING

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18. HEALTH OUTCOMES DATA SOURCE TABLES

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TABLE 18.1

SUMMARY OF COPD RELATED HEALTHCARE RESOURCE UTILIZATION BY PRIOR TREATMENT IN STUDIES 042/091 - ALL PATIENTS

PROTOCOL 040

PRIOR TREATMENT	UTILIZATION	NUMBER OF PATIENTS	NUMBER OF UTILIZATIONS
-----	-----	-----	-----
PLACEBO (N=243)	Physician Visit	110	365
	Er/Urgent Care	19	26
	Hospitalization	18	22
	ICU Admission	1	1
	TOTAL	113	402
SB 207499 (N=480)	Physician Visit	230	688
	Er/Urgent Care	39	56
	Hospitalization	37	48
	ICU Admission	1	2
	TOTAL	241	760

TABLE 18.2

SUMMARY OF COPD RELATED HEALTHCARE RESOURCE UTILIZATION RATE PER PATIENT YEAR OF FOLLOW-UP BY PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

PRIOR TREATMENT	RATE/PATIENT YEAR	%95 CI
-----	-----	-----
Placebo	0.983	(0.891, 1.084)
SB 207499	0.869	(0.810, 0.933)

1. RATE IS CALCULATED BY POISSON REGRESSION INCLUDING ONLY UTILIZATIONS OCCURRING DURING STUDY 040

TABLE 18.2

SUMMARY OF COPD RELATED HEALTHCARE RESOURCE UTILIZATION RATE PER PATIENT YEAR OF FOLLOW-UP BY PRIOR TREATMENT
IN STUDIES 042/091 - ALL PATIENTS
PROTOCOL 040

TRX	COUNT	DURATION	POISSON
PLACEBO	402	409.082	0.98269
SB 207499	759	873.123	0.86929

1. RATE IS CALCULATED BY POISSON REGRESSION INCLUDING ONLY UTILIZATIONS OCCURRING DURING STUDY 040

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TABLE 18.3

SUMMARY STATISTICS FOR PERCENT OF TIME IN HOSPITAL BY PRIOR TREATMENT IN STUDIES 042/091 - ALL PATIENTS

PROTOCOL 040

TREATMENT GROUP	N	MEAN	SEM	LOWER 95% CI	UPPER 95% CI
PLACEBO	18	1.472	1.791	-2.121	5.064
SB 207499	37	4.343	1.249	1.837	6.848

1. ONLY PATIENTS WITH A HOSPITALIZATION ARE INCLUDED IN THE ANALYSIS

TABLE 18.4

SUMMARY STATISTICS FOR PERCENT OF TIME IN ICU BY PRIOR TREATMENT IN STUDIES 042/091 - ALL PATIENTS

PROTOCOL 040

TREATMENT GROUP	N	MEAN	SEM	LOWER 95% CI	UPPER 95% CI
PLACEBO	1	3.371	0.000	.	.
SB 207499	1	5.548	0.000	.	.

1. ONLY PATIENTS WITH A HOSPITALIZATION ARE INCLUDED IN THE ANALYSIS



SB 207499

TABLE 18.5

SUMMARY STATISTICS FOR PERCENT OF DAYS LOST FROM WORK BY PRIOR TREATMENT IN STUDIES 042/091 - ALL PATIENTS

PROTOCOL 040

TREATMENT GROUP	N	MEAN	SEM	LOWER 95% CI	UPPER 95% CI
-----	----	-----	-----	-----	-----
PLACEBO	5	1.388	6.960	-13.65	16.424
SB 207499	10	8.427	4.922	-2.205	19.060

1. ONLY PATIENTS WITH A HOSPITALIZATION ARE INCLUDED IN THE ANALYSIS

19. Source Figures

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Figure 19.1
Mean (SEM) Change from Baseline in FEV1(L) - All Patients
Protocol 040

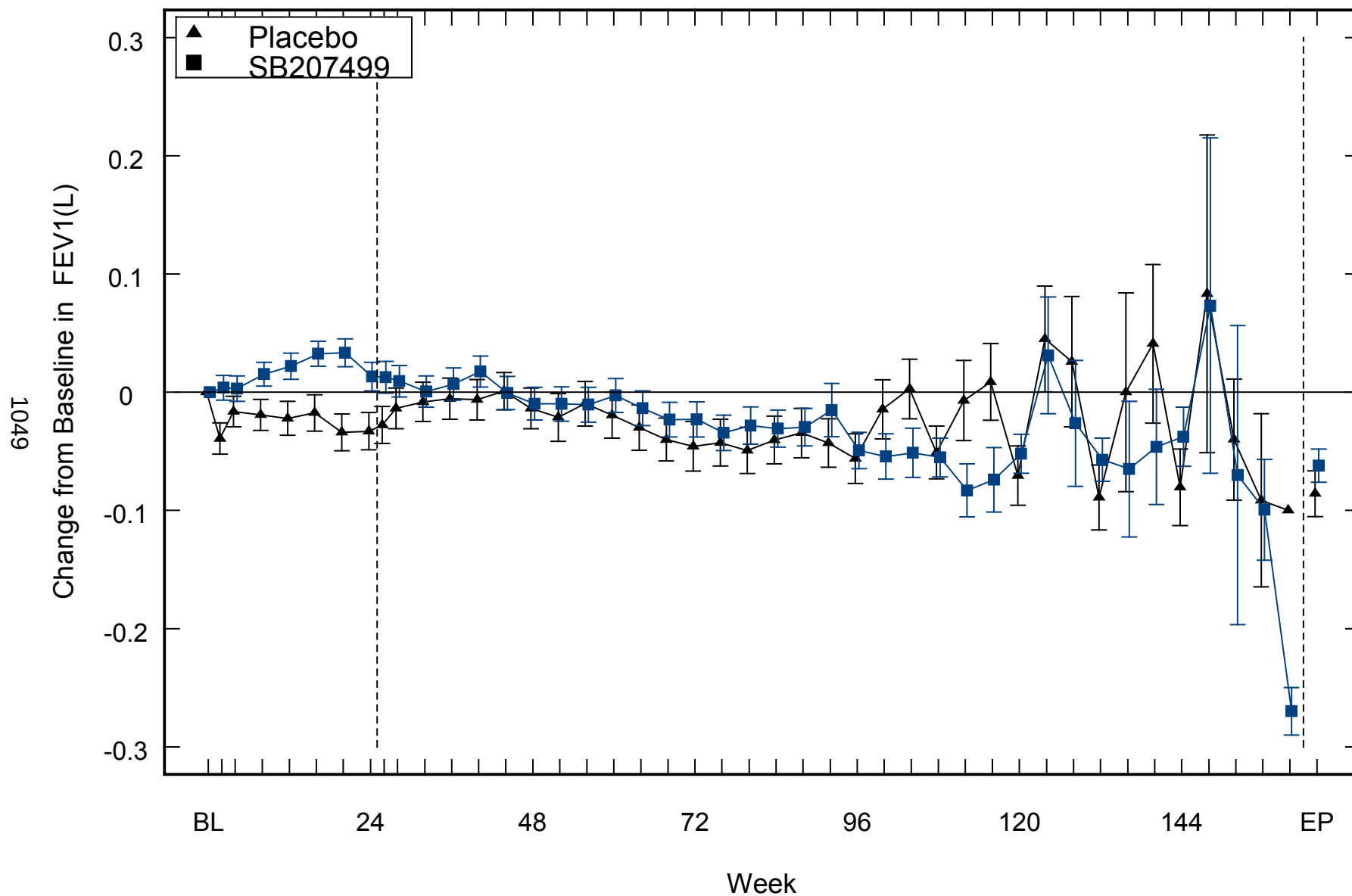


Figure 19.2
Mean (SEM) Change from Baseline in FVC(L) - All Patients
Protocol 040

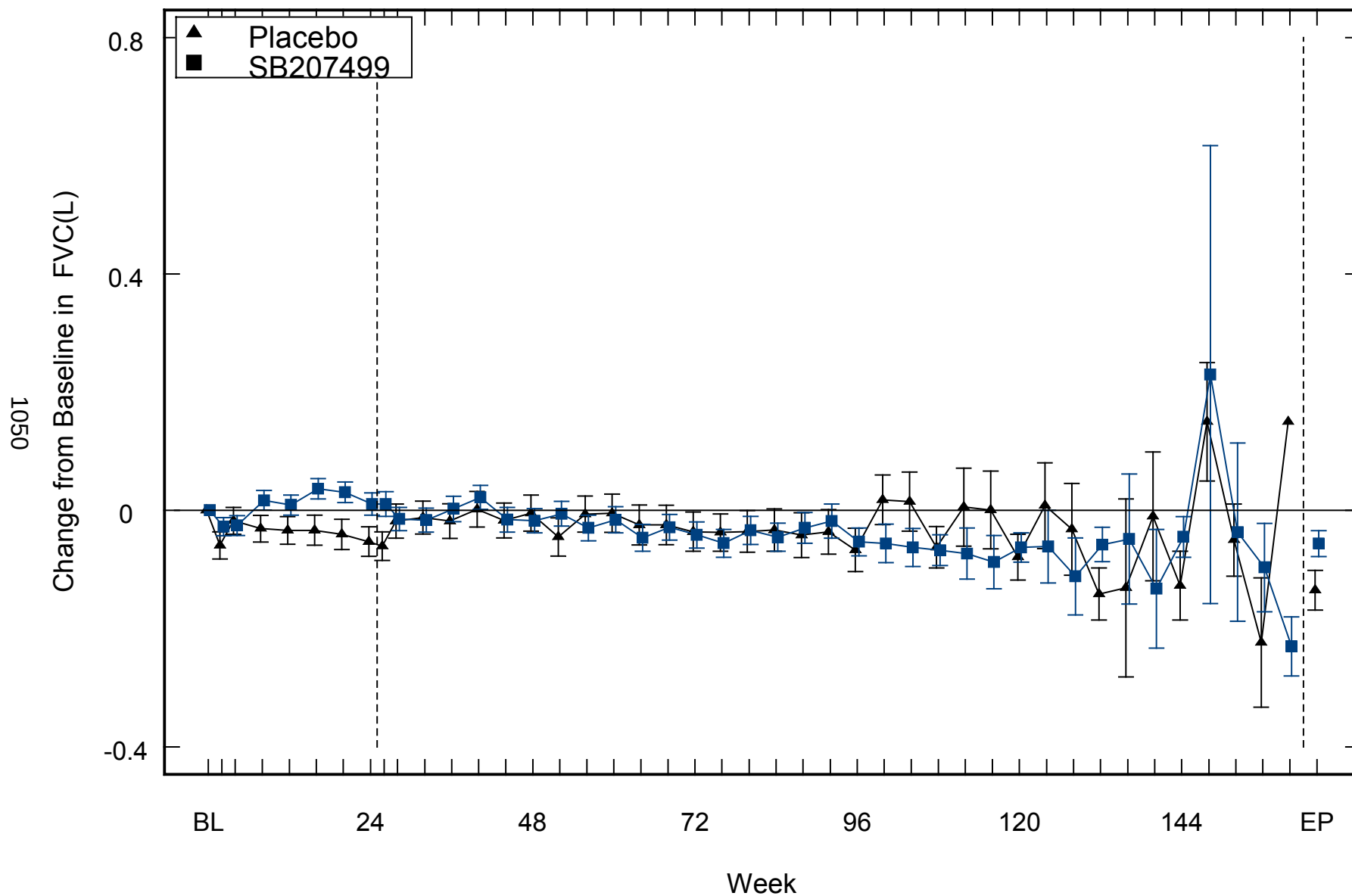


Figure 19.3
Mean (SEM) Change from Baseline in PEFR(L/MIN) - All Patients
Protocol 040

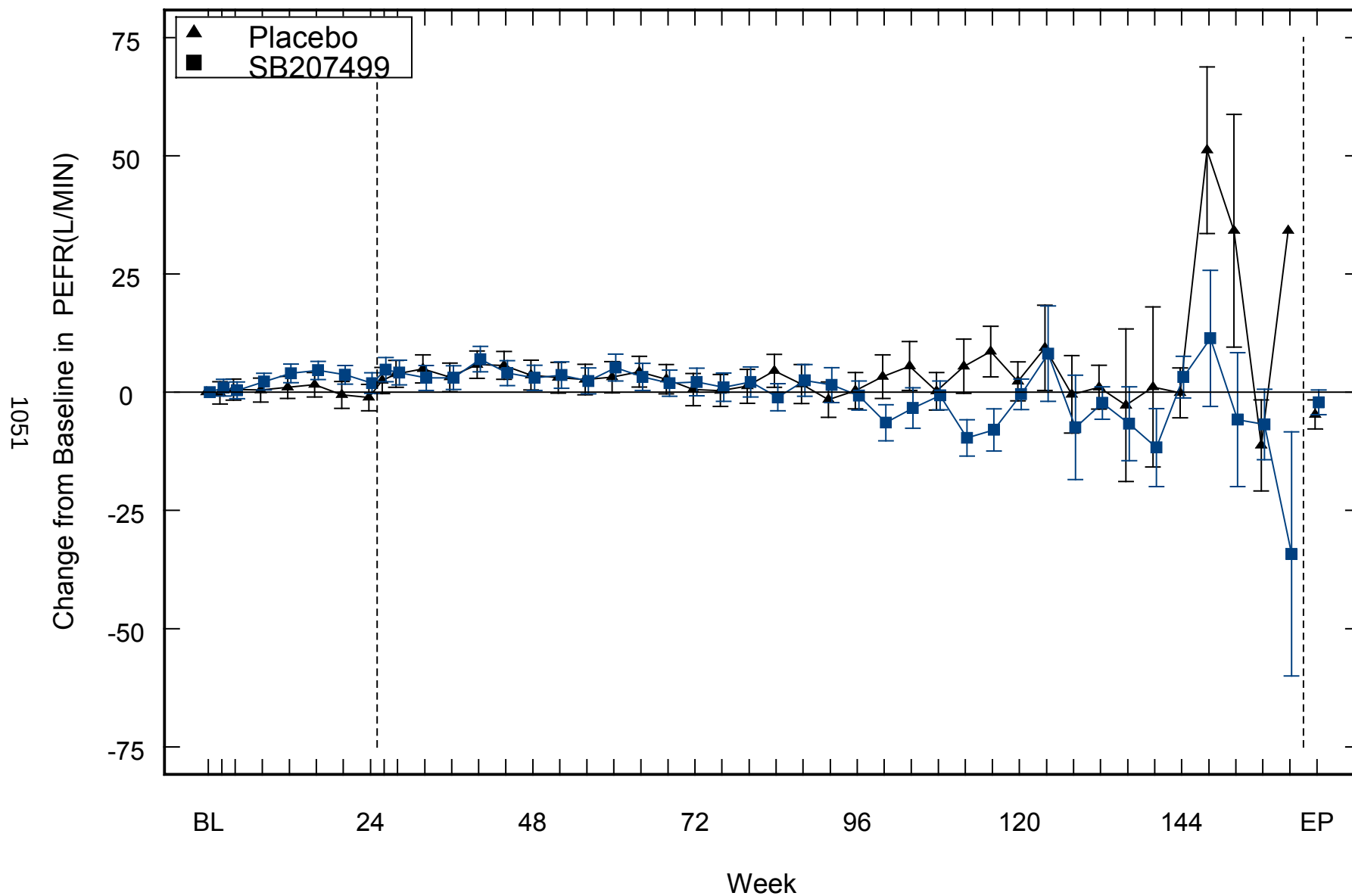
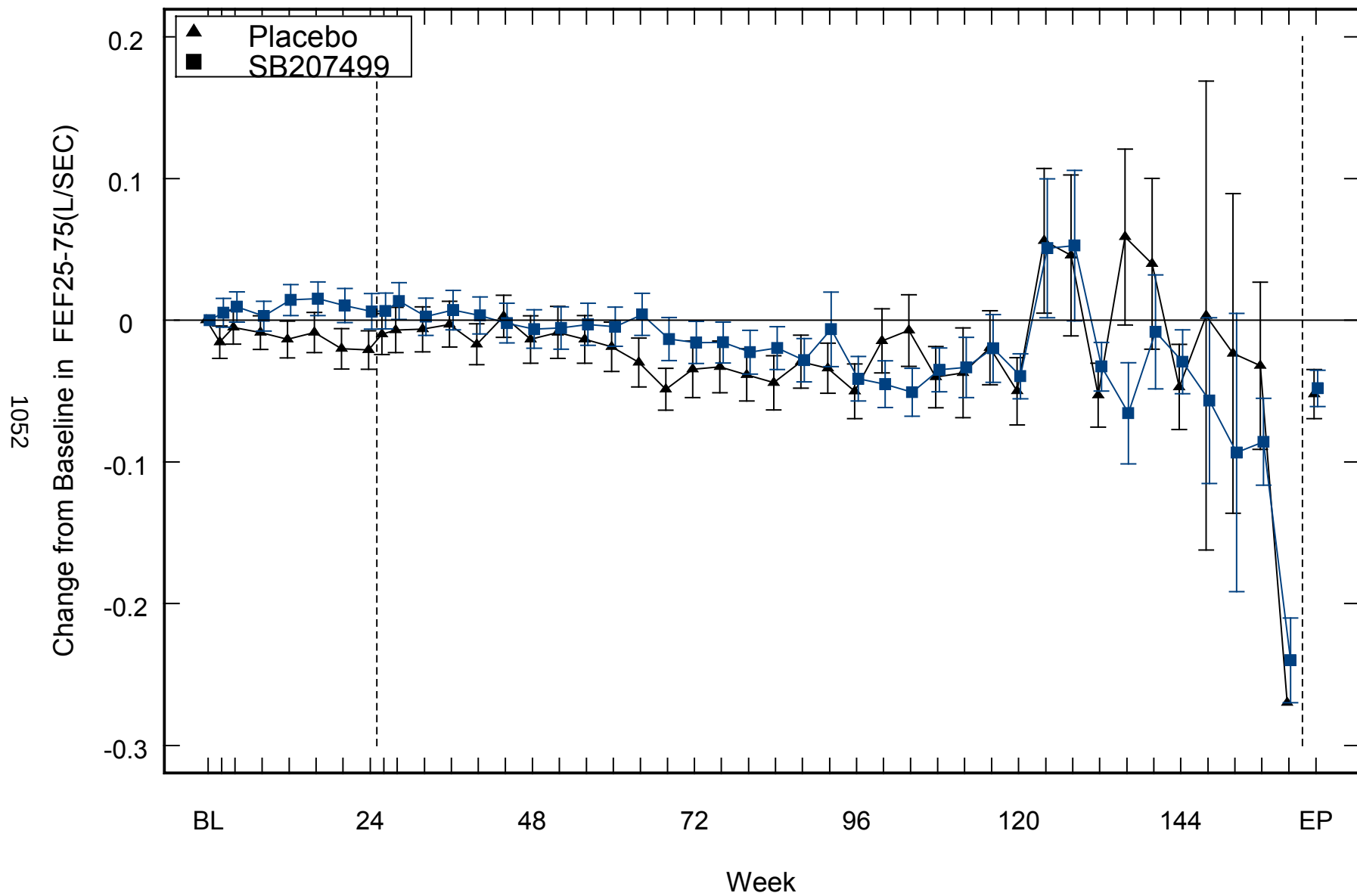


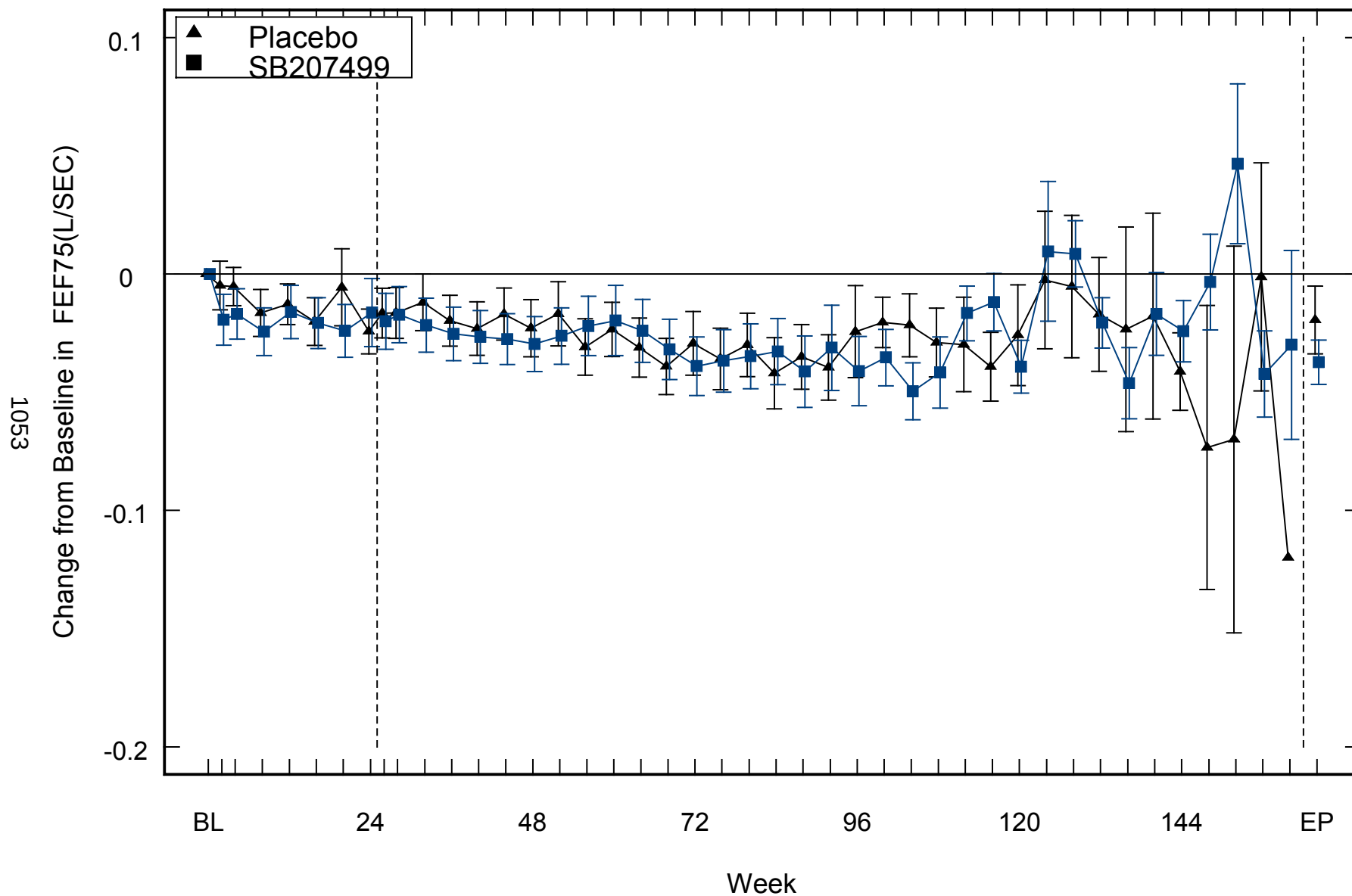
Figure 19.4
Mean (SEM) Change from Baseline in FEF25-75(L/SEC) - All Patients
Protocol 040



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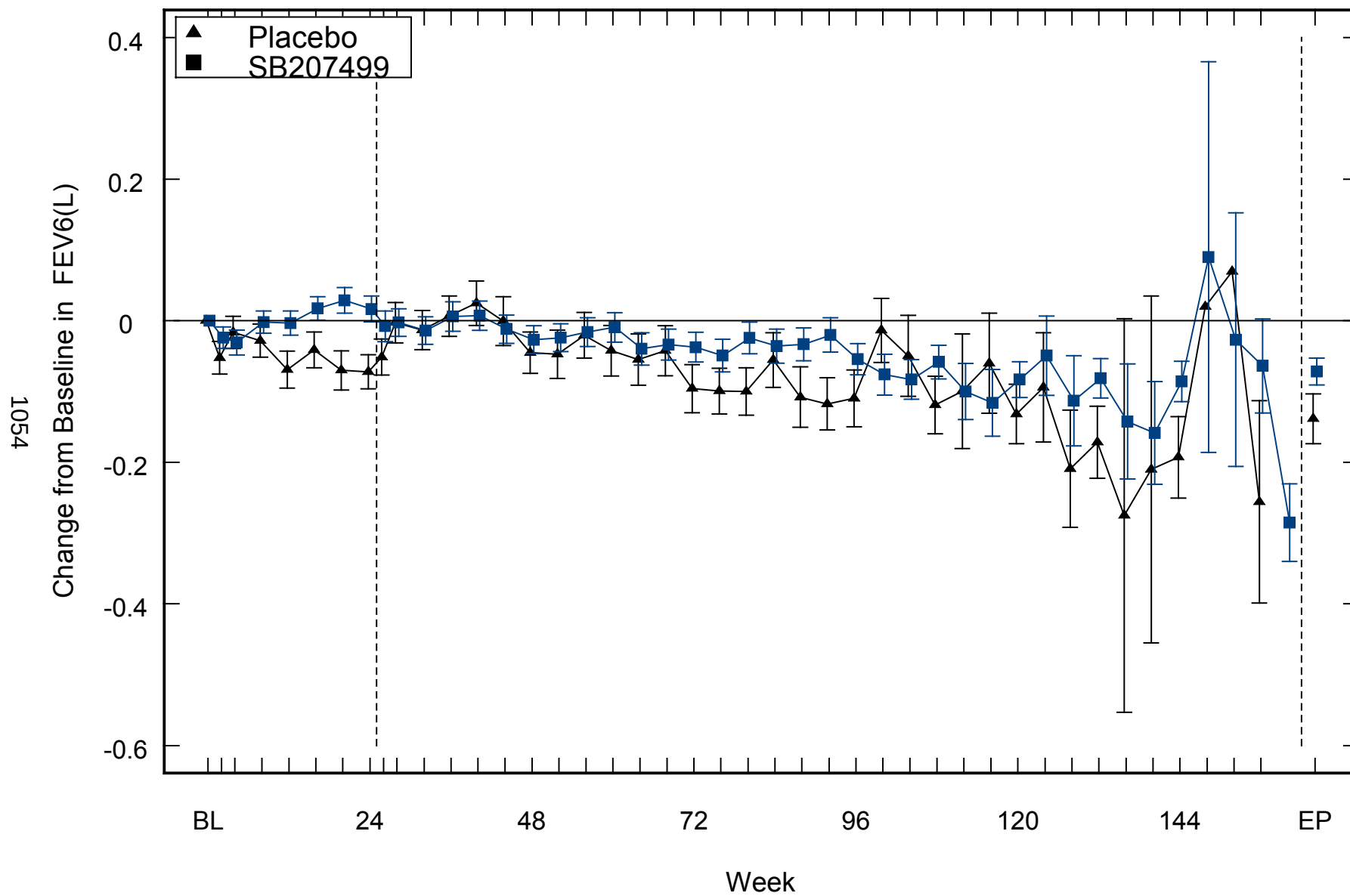
Figure 19.5
Mean (SEM) Change from Baseline in FEF75(L/SEC) - All Patients
Protocol 040



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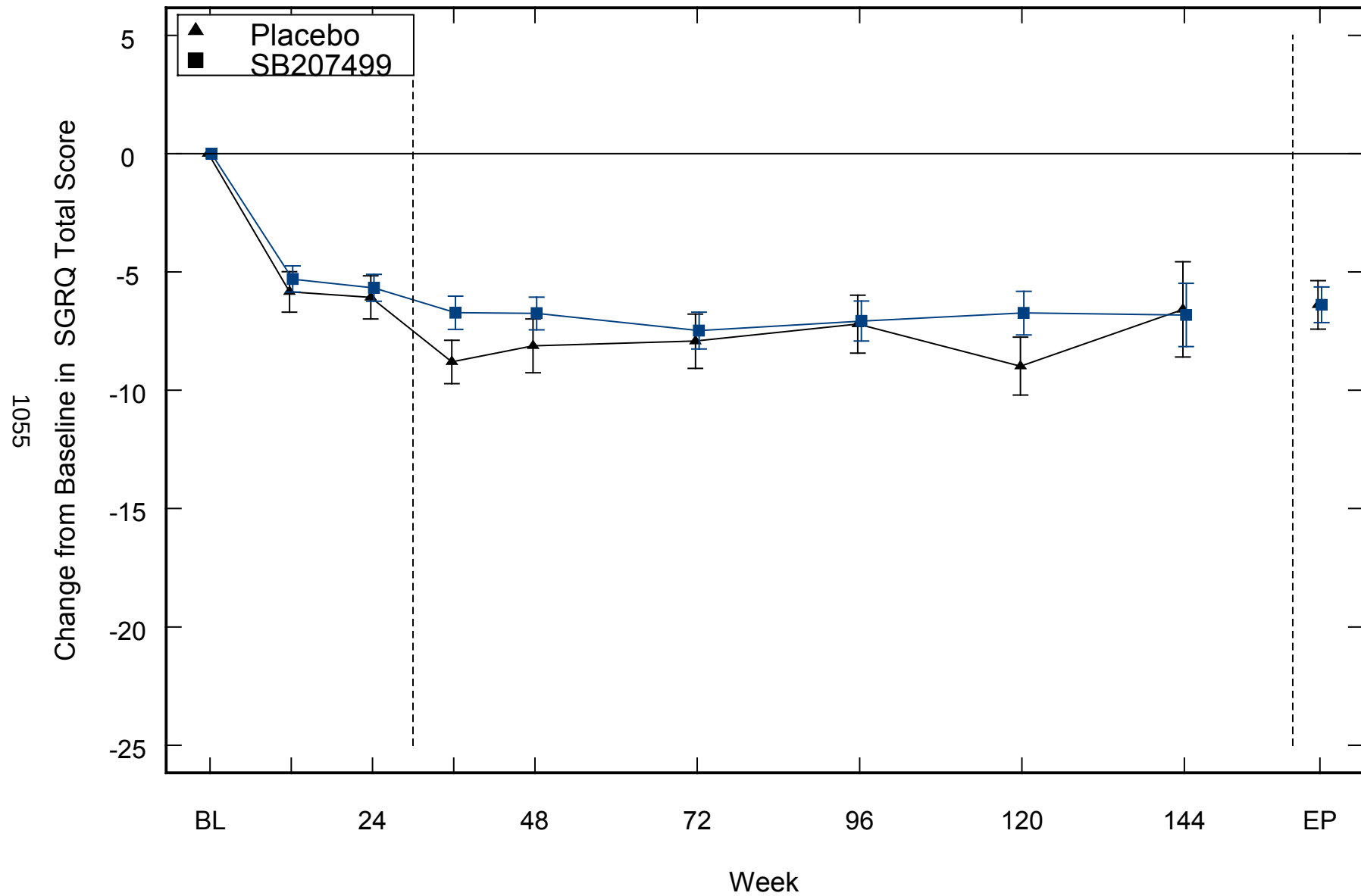
Figure 19.6
Mean (SEM) Change from Baseline in FEV6(L) - All Patients
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Figure 19.7
Mean (SEM) Change from Baseline in SGRQ Total Score - All Patients
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Figure 19.8
Mean (SEM) Change from Baseline in SGRQ Symptoms Score - All Patients
Protocol 040

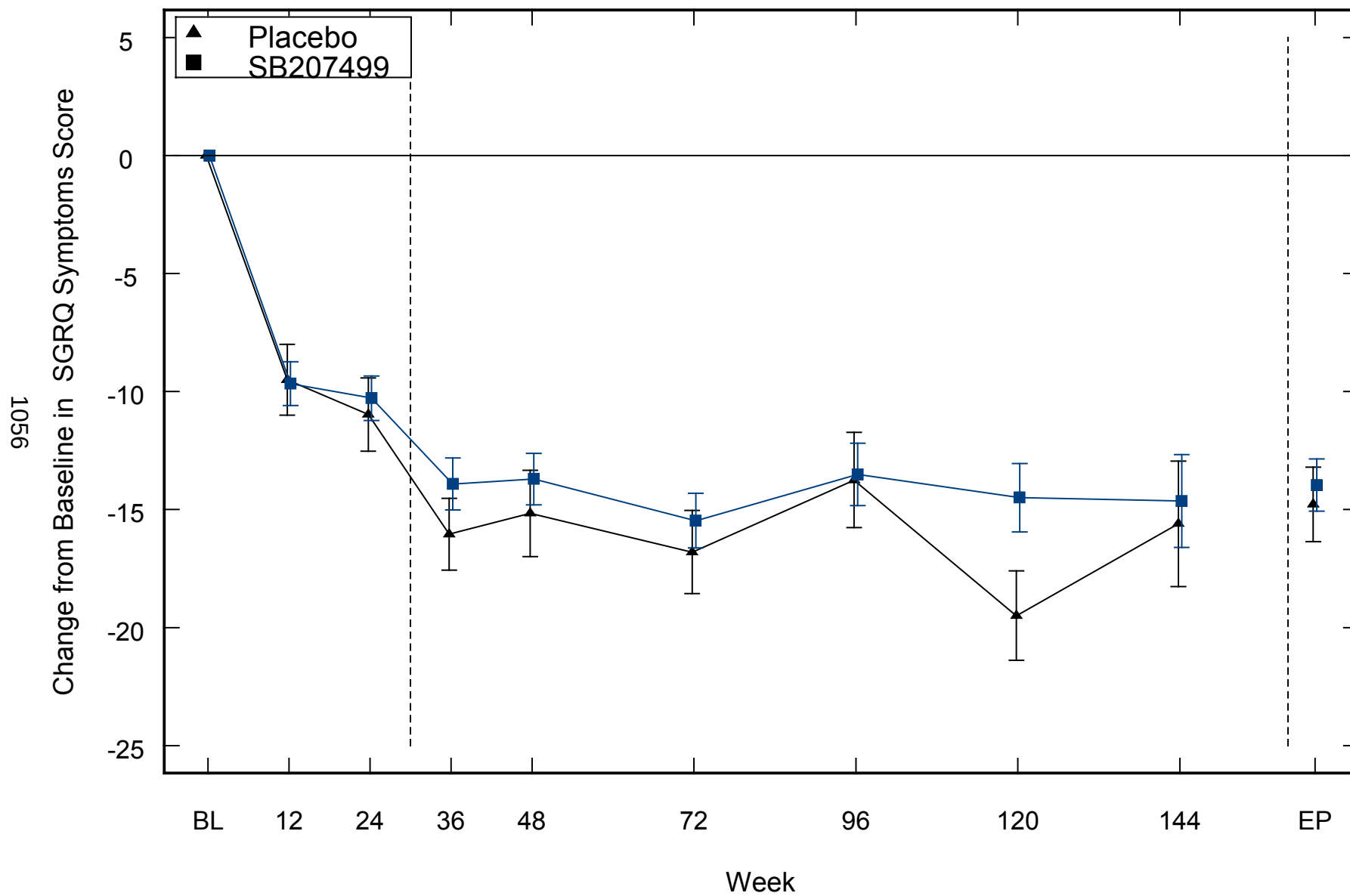
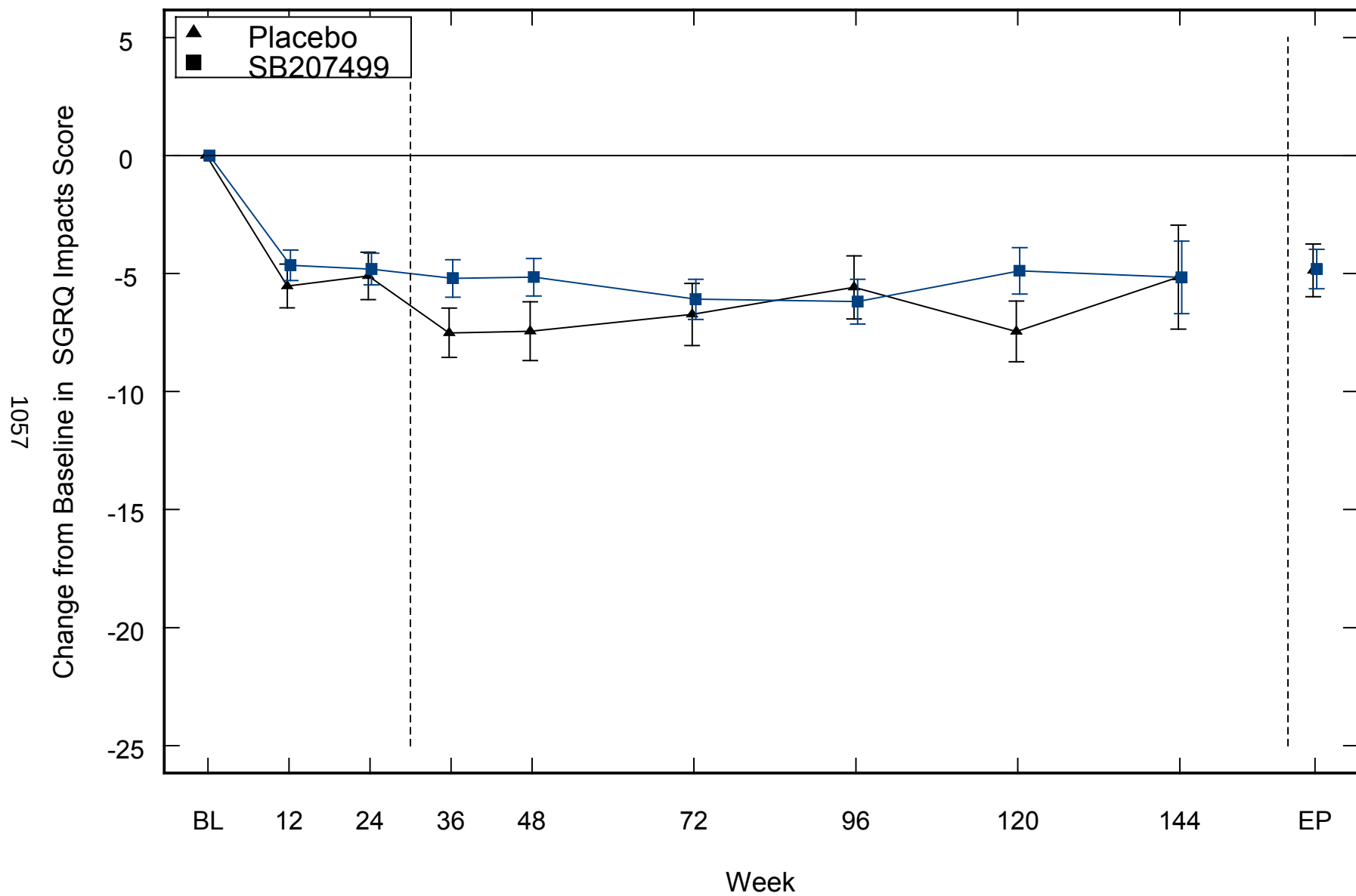


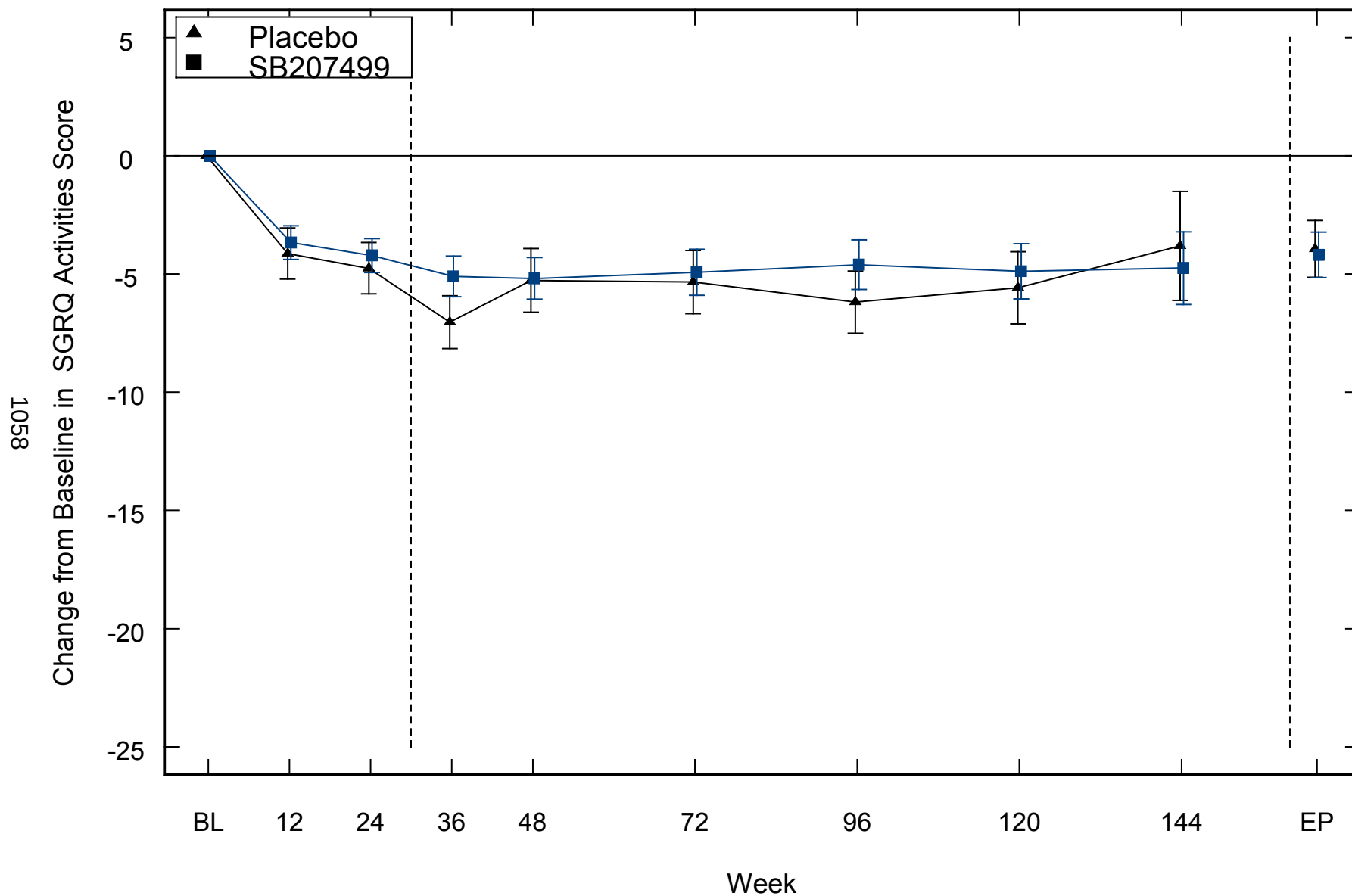
Figure 19.9
Mean (SEM) Change from Baseline in SGRQ Impacts Score - All Patients
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Figure 19.10
Mean (SEM) Change from Baseline in SGRQ Activities Score - All Patients
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Figure 19.11
Mean (SEM) Change from Baseline in Overall Dyspnea Score - All Patients
Protocol 040

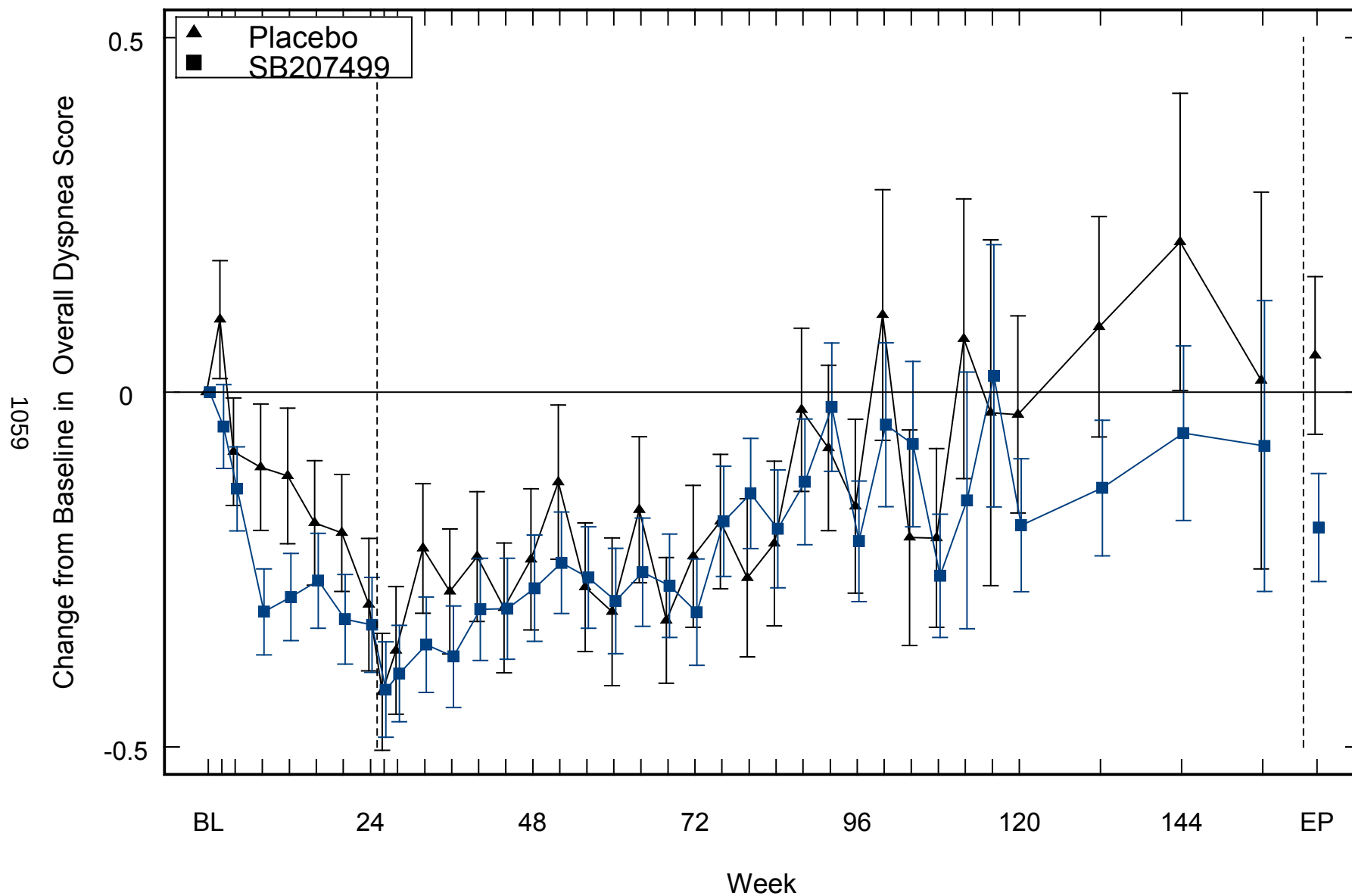


Figure 19.12
Mean (SEM) Change from Baseline in Post-Exercise Dyspnea Score - All Patients
Protocol 040

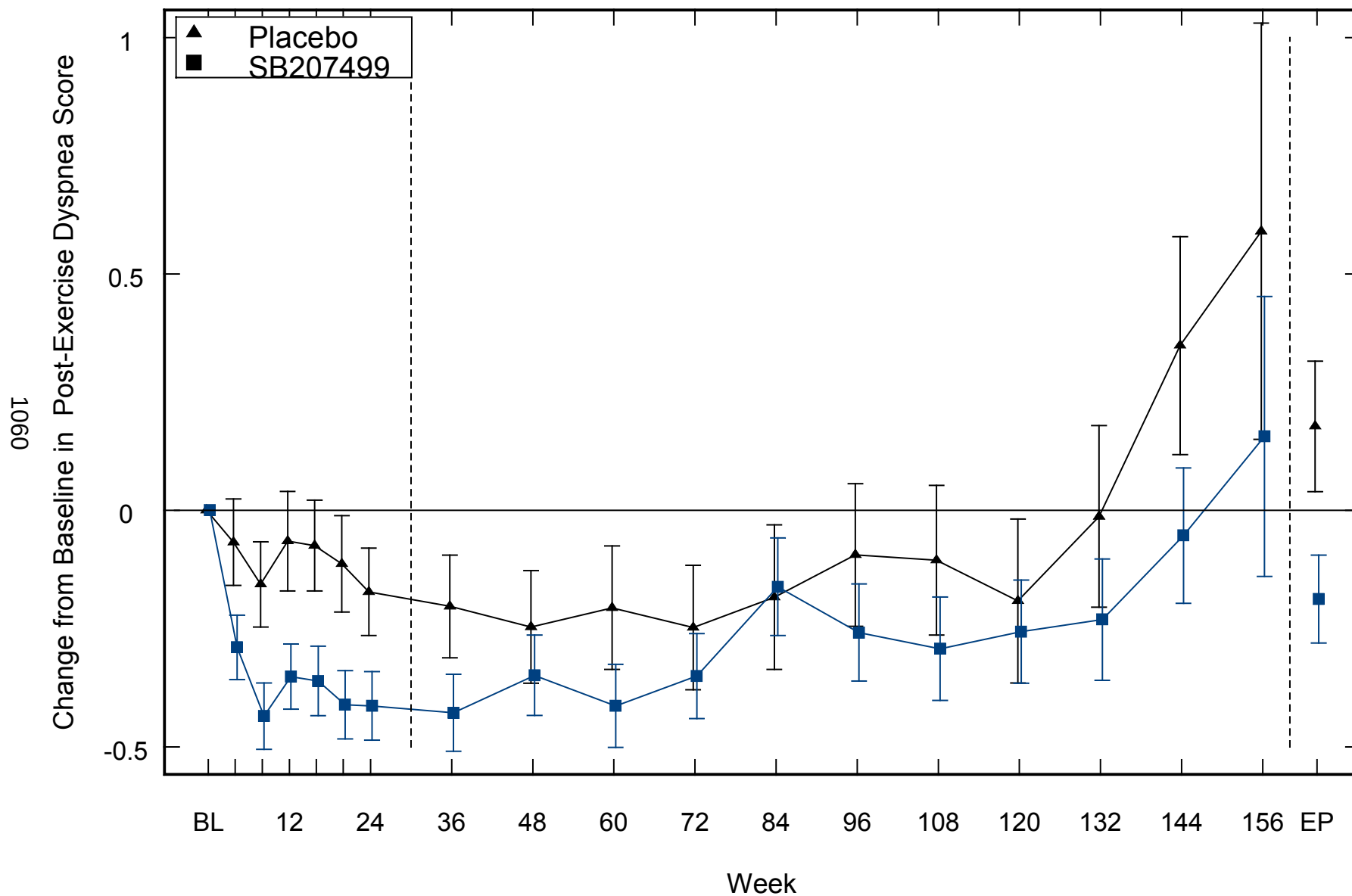
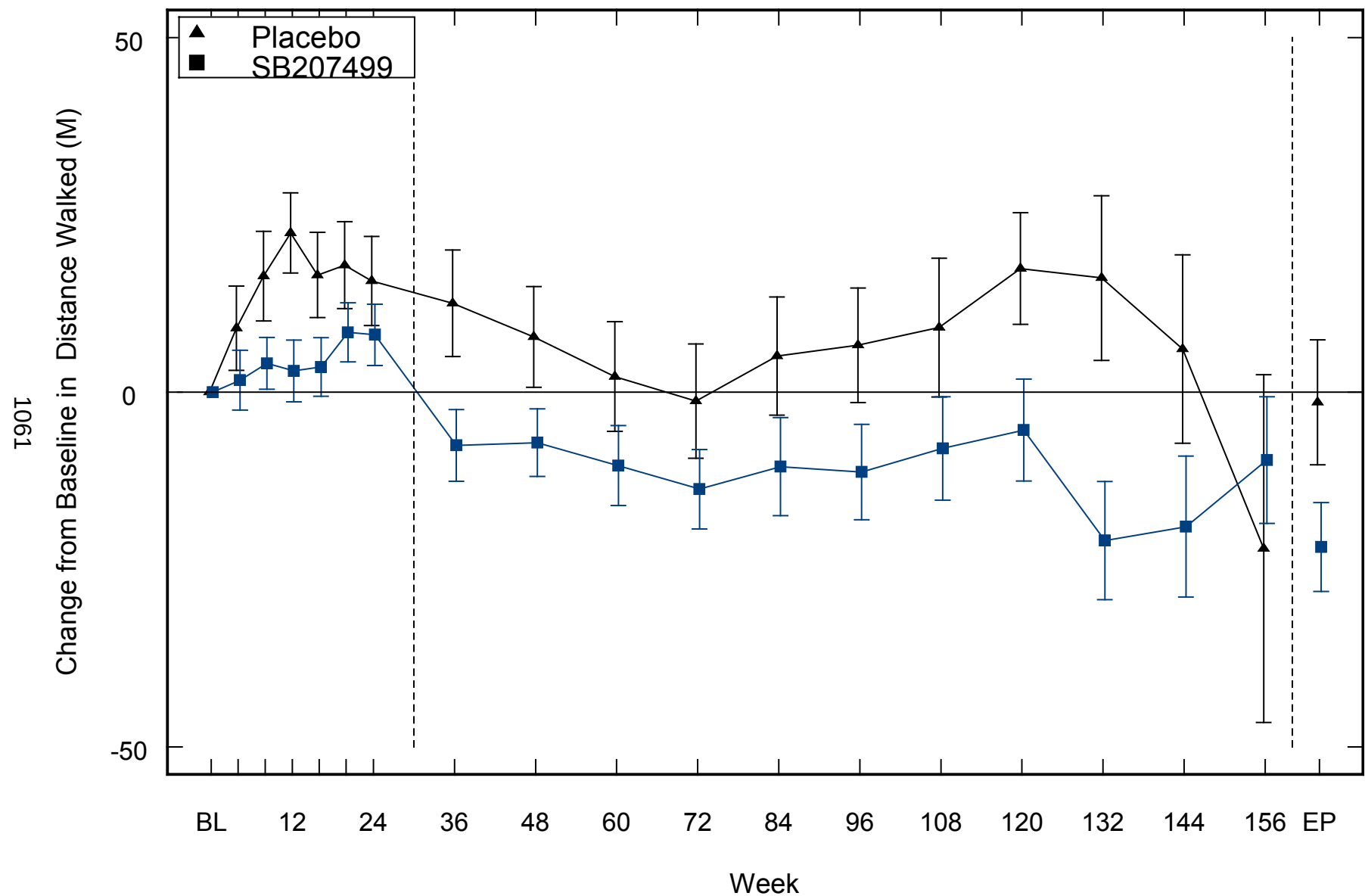


Figure 19.13
Mean (SEM) Change from Baseline in Distance Walked (M) - All Patients
Protocol 040



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Figure 19.14
Mean (SEM) Change from Baseline in SF-36 Physical Composite Score - All Patients
Protocol 040

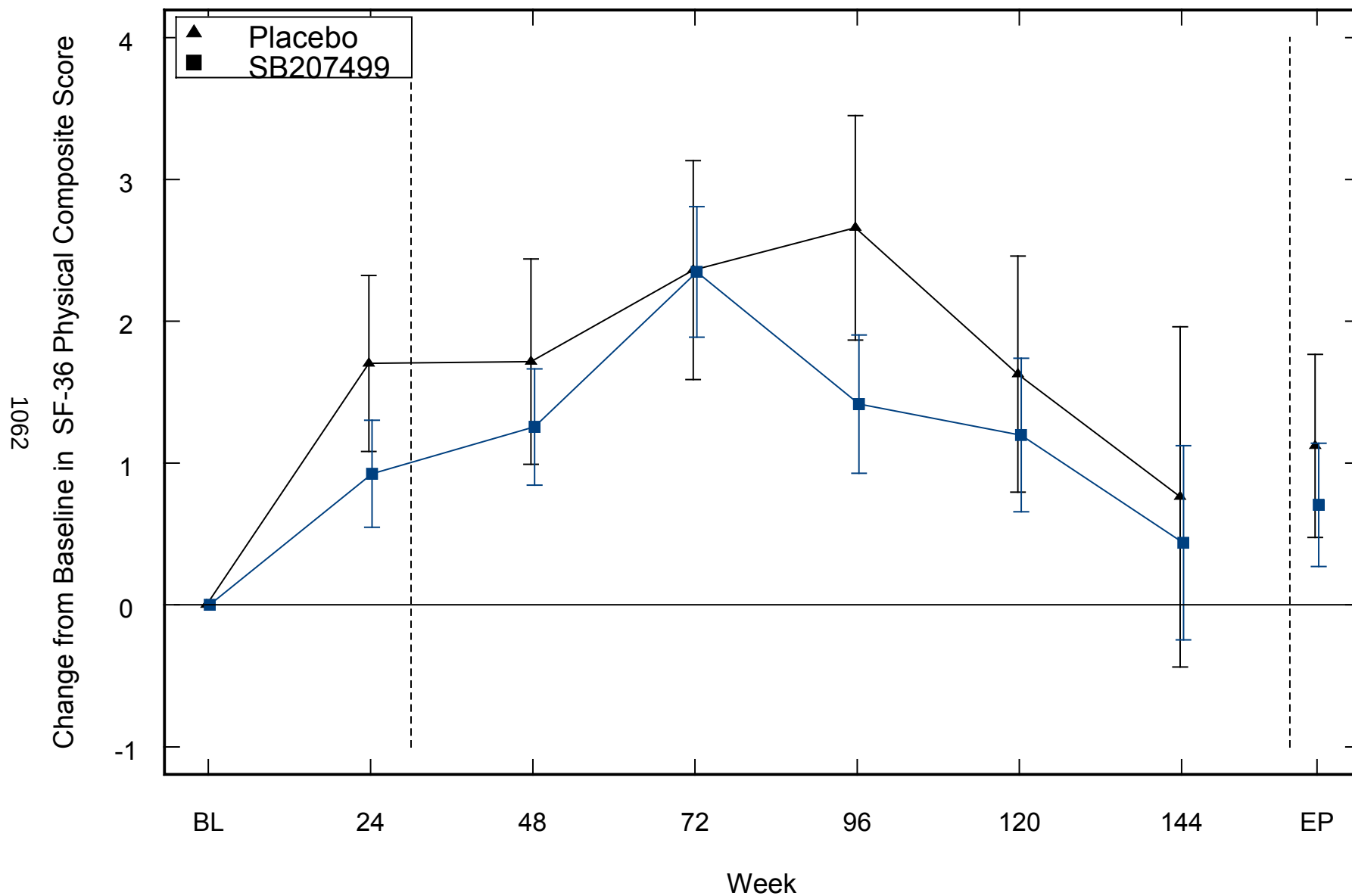


Figure 19.15 Cumulative Incidence of Nausea
By Time of Initial Onset and Prior Treatment in Studies 042 or 091
Protocol 040

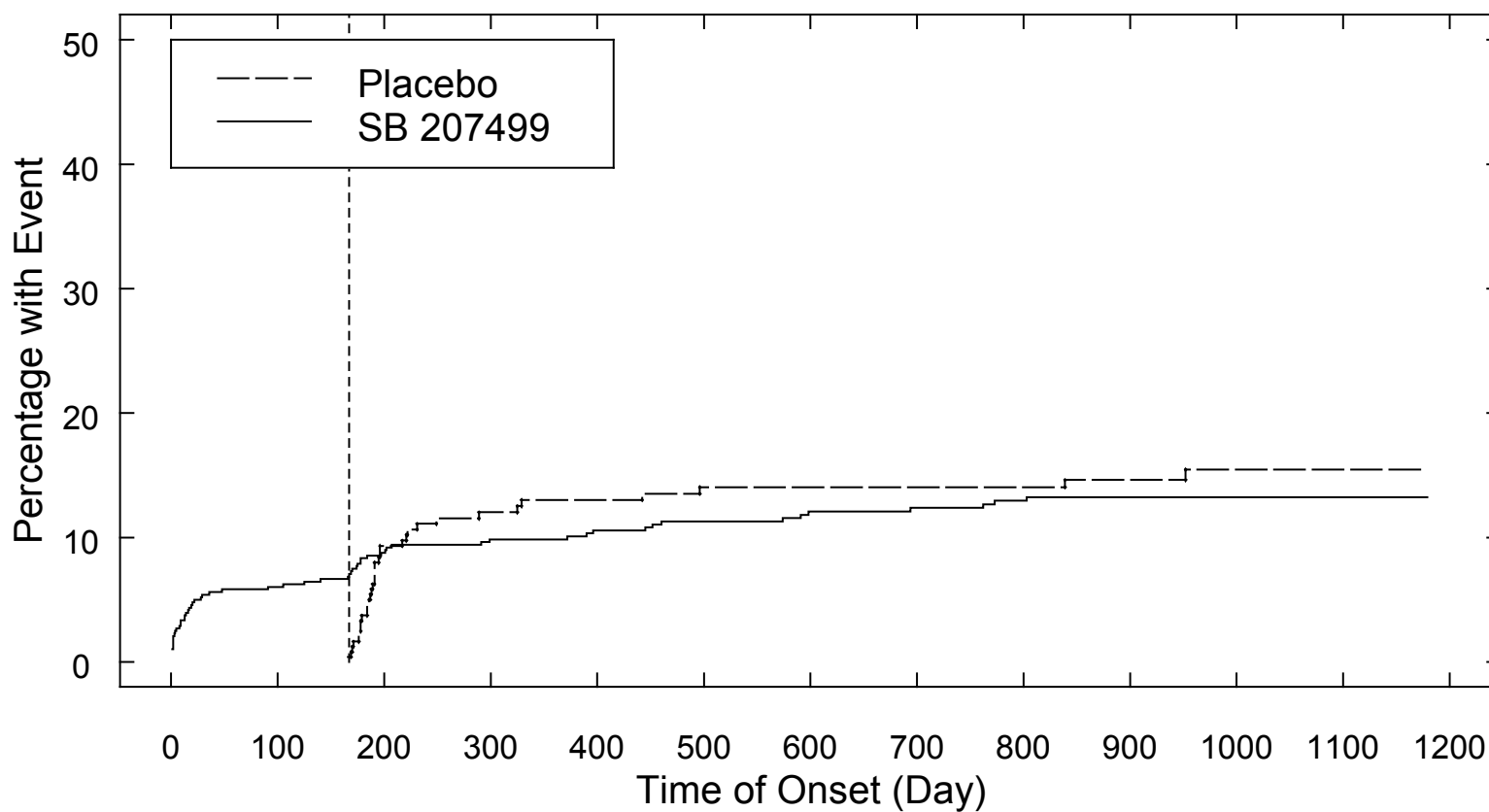


Figure 19.16 Cumulative Incidence of Abdominal Pain
By Time of Initial Onset and Prior Treatment in Studies 042 or 091
Protocol 040

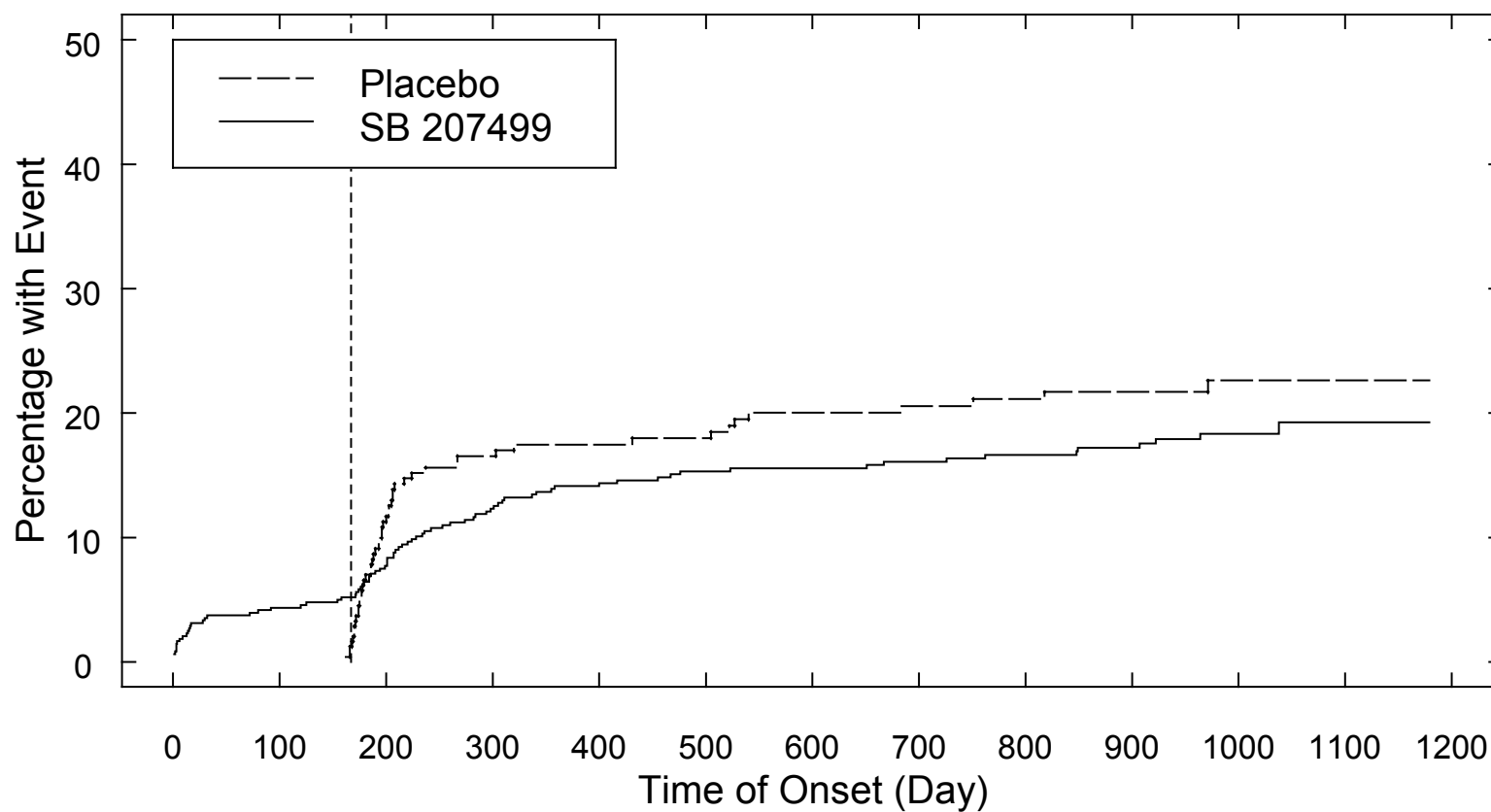
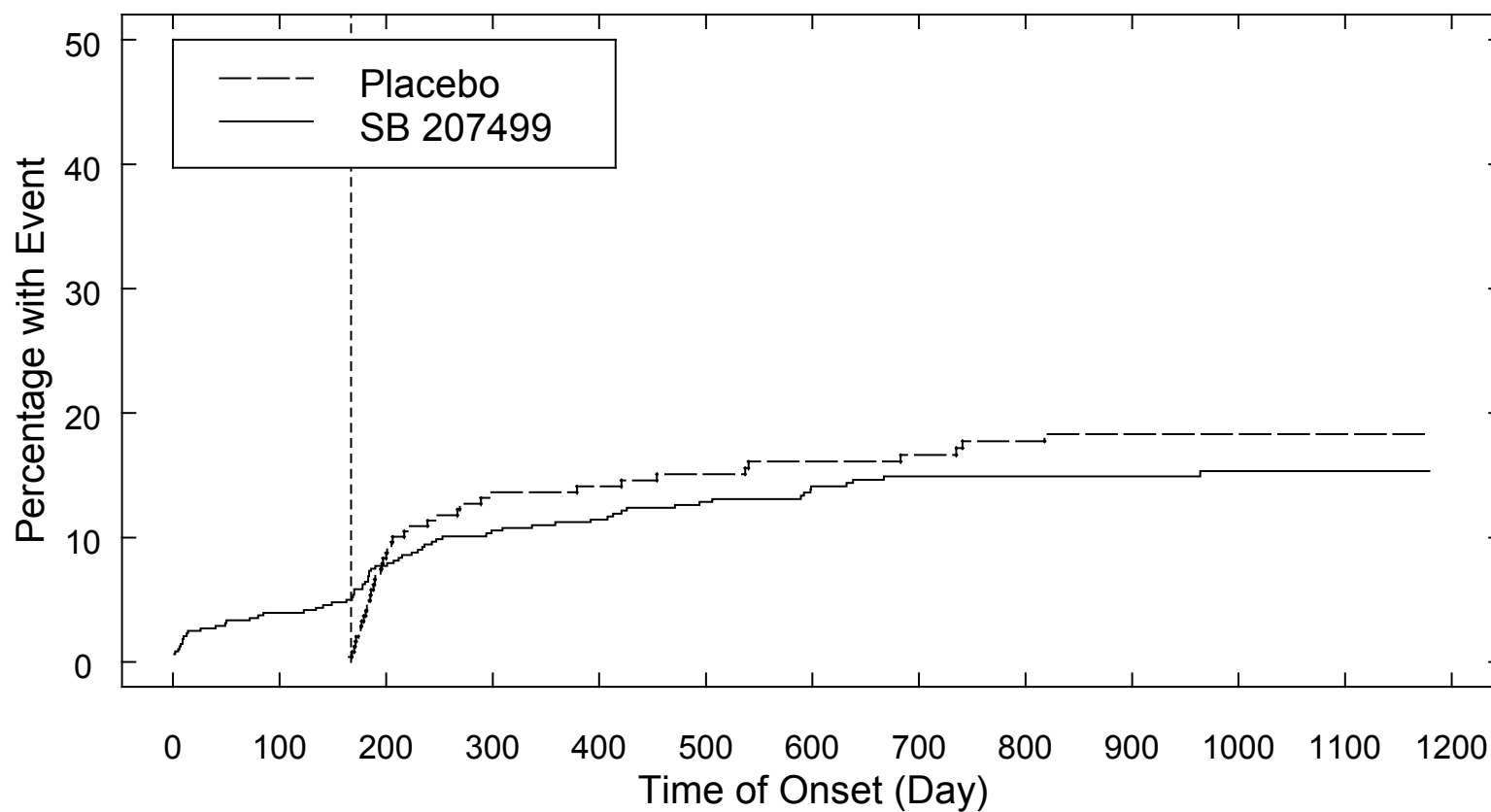


Figure 19.17 Cumulative Incidence of GI Adverse Experiences of Concern
By Time of Initial Onset and Prior Treatment in Studies 042 or 091
Protocol 040



20. CASE NARRATIVES



SmithKline Beecham

A Multicentre, Open-label Extension Study to Evaluate the Safety, Tolerability and Efficacy of Oral SB 207499 (15 mg twice daily) in Patients with Chronic Obstructive Pulmonary Disease (COPD)

FINAL PROTOCOL – Excluding Norway

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Issue Date:	12 March 1999
Amend 1:	19 August 1999 (Norway specific)
Amend 2:	15 November 2000 (not applicable to Norway)
Amend 3:	23 February 2001 (Norway specific – rejected)
Amend 4:	12 April 2001

Endorsements



Clinical Unit: Cardiopulmonary Therapeutic Team

Document No.: SB-207499/RSD-100TJW/3

Compound No: SB 207499

Protocol Title: A Multicentre, Open-label Extension Study to Evaluate the Safety, Tolerability and Efficacy of Oral SB 207499 (15 mg twice daily) in Patients with Chronic Obstructive Pulmonary Disease (COPD)

CPMS Number: 207499/040

SB Medical Monitor: Dr [REDACTED]

I, the undersigned, have reviewed this protocol, including Appendices, and I will conduct the clinical study as described and will adhere to the Ethical and Regulatory Considerations stated. I have read and understood the contents of the Investigator Brochure.

Investigator Signature

Date

Print Investigator Name

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List of Abbreviations & Definitions

Abbreviations

AE	adverse experience
ALP	alkaline phosphatase
ALAT (SGPT)	alanine aminotransferase
ASAT (SGOT)	aspartate aminotransferase
bid	twice daily
BP	blood pressure
bpm	beats per minute
BTPS	body temperature and pressure standard
BUN	blood urea nitrogen
cyclic AMP	cyclic adenosine monophosphate
CI	confidence interval
cm	centimetre
COPD	chronic obstructive pulmonary disease
CRF	case report form
DLCO	carbon monoxide diffusing capacity
ECG	electrocardiogram
ERC	ethics review committee
FEF ₂₅₋₇₅	forced expiratory flow at 25-75% vital capacity
FEF ₇₅	forced expiratory flow at 75% vital capacity
FEV ₁	forced expiratory volume in 1 second
FEV ₆	forced expiratory volume in 6 seconds
FVC	forced vital capacity
GCP	good clinical practice
GGT	gamma-glutamyl transferase
hr	hour
HR	heart rate
IRB	institutional review board
IU	international unit
IUD	intrauterine device
kg	kilogram
L	litre
mcg	microgram
mg	milligram
min	minute
mL	millilitre
mmHg	millimetres of mercury
mmol	millimoles
ms	milliseconds
NA	not applicable
ng	nanogram
PDE4	phosphodiesterase 4
PEFR	peak expiratory flow rate

PFT	pulmonary function test
prn	pro re nata (as needed)
R&D	research and development
RBC	red blood cell count
s	second
SB	SmithKline Beecham
SBCL	SmithKline Beecham Clinical Laboratories
SBP	systolic blood pressure
SF-36	short form survey 36
SGRQ	St. George's Hospital Respiratory Questionnaire
SOP	standard operating procedure
uL	microlitre
V	visit
WBC	white blood cell count
WHO	World Health Organisation
wks	weeks

Definitions

adverse experience	includes any noxious, pathologic or unintended change in anatomical, physiologic or metabolic functions as indicated by physical signs, symptoms and/or laboratory changes occurring in any phase of the clinical trial whether or not considered drug related
serious adverse experience	any experience which is fatal, life-threatening, permanently or temporarily disabling or incapacitating or results in hospitalisation, prolongs a hospital stay or is associated with cancer or overdose (either accidental or intentional). In addition, any experience which the Investigator regarded as serious or which suggested any significant hazard, contraindication, side effect or precaution that may have been associated with the use of the drug was reported as serious

Synopsis

Compound/Protocol No.

SB 207499/040

Protocol Title

A multicentre, open-label extension study to evaluate the safety, tolerability and efficacy of oral SB 207499(15 mg twice daily) in patients with chronic obstructive pulmonary disease (COPD).

Rationale

COPD is a disorder characterised by reduced maximum expiratory flow and slow forced emptying of the lungs, features which do not change markedly over several months. It is a major cause of morbidity and mortality. The fixed airflow limitation in COPD is thought to be due to three conditions: chronic bronchitis, emphysema and small airways disease. The airflow obstruction is progressive in nature, mostly irreversible, and may be accompanied by airway hyperreactivity.

The rationale for the use of PDE₄ inhibitors in the treatment of COPD is based upon the role of cyclic adenosine monophosphate (cyclic AMP) as a second messenger that mediates a broad suppression of immune and inflammatory cell activity. SB 207499 has been shown to have marked anti-inflammatory and bronchodilatory activity in multiple *in vitro* and *in vivo* settings. Consequently, PDE₄ inhibitors such as SB 207499 could represent important new treatments for COPD.

In support of the asthma and COPD clinical programs, 13 Phase I studies have been completed to characterise the safety, tolerability, pharmacokinetics and potential drug interaction profile of SB 207499. A total of 1547 patients have been enrolled into eight Phase II clinical trials designed to explore the safety and efficacy of a range of doses of SB 207499. Six studies were conducted in asthmatic patient populations, and two studies in patients with COPD. In COPD study 032, treatment with SB 207499 15 mg bid was clinically and statistically superior to placebo with respect to improvements in pulmonary function parameters. Clinically significant improvements in dyspnoea, beta₂-agonist use and quality of life were also observed. SB 207499 (repeat dosing up to 15 mg bid) was generally well tolerated in the Phase II program.

Headache and nausea were the adverse experiences most commonly associated with treatment with SB 207499, though these events tended to have been reported as mild, and infrequently led to withdrawal. Generally, the onset of nausea has been early during treatment. No obvious effects on laboratory abnormalities, ECGs or vital signs have been observed.

The Phase III COPD program consists of three 6-month randomised, double-blind efficacy and safety trials. Patients completing these studies will have the option of receiving open label medication with SB 207499 (15 mg bid) in one of two extension studies (studies 040 – Europe, South Africa and Australia/New Zealand and 041 – US and Canada). The present study, study 040, is intended to evaluate the long-term safety of SB 207499 (15 mg bid) and to explore the long term efficacy of the compound. Prior to enrolment in study 040, patients must have completed study 042 or study 091 where patients received SB 207499 15 mg bid or placebo for 24 weeks in study 042 and 26 weeks in study 091.

Objective(s)

- To evaluate the long-term safety and tolerability of SB 207499 (15 mg bid) in patients with COPD.
- To further evaluate clinical efficacy of SB 207499 in terms of pulmonary function, disease symptoms and quality of life.

Study Population

The study population will consist of males and females with COPD, who have successfully completed study 042 or study 091 in accordance with the protocol. Approximately 600 patients are expected to be enrolled in the study. Approximately 200 centres within Europe, South Africa and Australia/New Zealand are expected to participate.

Study Design

This study is an open-label extension study, designed to assess the long-term safety, tolerability and efficacy of SB 207499 15 mg bid. This study is open to patients who have completed study 042 or study 091 in accordance with the protocol (including all assessments at the last double-blind visit). Patients entering the extension study will be required to attend two weekly visits, one biweekly visit and then visits at 4-week intervals until at least Week 48, followed by 12-weekly visits until termination of the study or withdrawal of

the patient. The study will continue until the compound is registered or the project is terminated by the sponsor. Eligible patients must give written informed consent and meet the additional inclusion/ exclusion criteria for entry into study 040.

There are no restrictions on the use of any concomitant COPD medications (with the exception of theophylline and aminophylline) during this study.

Safety Parameters

- Adverse experiences including additional monitoring for gastrointestinal adverse experiences
- Laboratory safety data
- 12 lead ECG parameters
- Vital signs
- Physical examination including respiratory examination

Efficacy Parameters

- Pulmonary function tests (FEV₁, FEV₆, FEF₂₅₋₇₅, FEF₇₅, FVC, PEF_R)
- Exercise tolerance test (6-minute walk test)
- Dyspnoea assessments (modified Borg scale) at rest to assess overall dyspnoea since the last visit and after exercise tolerance test
- COPD exacerbation rates
- Quality of life assessments
- Healthcare utilisation

Study Procedure

Patients will be assessed for their eligibility for study 040 at their final scheduled visit (prior to Safety Follow-up visit) in study 042 or study 091. Eligible patients will receive SB 207499 at a dose of 15 mg bid for the duration of the study. The study blind from the previous study will not be broken before entering patients into study 040. With the exception of

theophylline or aminophylline (oral or intravenous) other COPD medication is permitted to be used concomitantly with SB 207499.

Assessment Schedule:

Safety: Adverse experiences, resting 12-lead ECG parameters, vital signs and laboratory tests will be recorded at every visit. Additional monitoring for gastrointestinal adverse experiences will be measured at 24 weeks, 48 weeks and annually thereafter.

Efficacy: Pulmonary function tests will be measured at every visit except Visit 2. COPD exacerbation assessment and healthcare utilisation will be recorded at every visit. Overall breathlessness (modified Borg) will be performed at every visit except Visit 2. Exercise tolerance test (6-minute walk) will be performed at Visits 1, 6, 9, 12 and 15 and then every 12 weeks. Quality of life assessments (SGRQ and SF-36) will be recorded at Visits 1, 9 and 15 and then every 24 weeks (An additional SGRQ assessment will be performed at Visit 6).

Statistical Evaluation

This is a phase III open-label trial with the primary purpose of evaluating patient safety. No formal power calculations were performed.

Descriptive statistics including 95% confidence intervals will be provided for the change from baseline of each serially collected efficacy parameter. Baseline will be defined as the predose assessment at the randomisation visit of the parent studies, 042 and 091. For patients randomised to placebo in study 042 or study 091 additional analyses will be performed based on the change from the final assessments prior to dosing in study 040.

All efficacy analyses will be based on the population of patients receiving at least one dose of study medication and having an assessment of efficacy in the study.

Safety analyses will be based on all patients receiving at least one dose of study medication. Summaries of adverse experiences, ECGs, vital signs, and clinical laboratories will be provided.

1.0 Introduction

SB 207499 is a potent and selective phosphodiesterase type 4 (PDE₄) inhibitor currently under development for the treatment of asthma and chronic obstructive pulmonary disease (COPD).

COPD is a disorder characterised by reduced maximum expiratory flow and slow forced emptying of the lungs, features which do not change markedly over several months. [2] It is a major cause of morbidity and mortality. The fixed airflow limitation in COPD is thought to be due to three conditions: chronic bronchitis, emphysema and small airways disease. The airflow obstruction is progressive in nature, mostly irreversible, and may be accompanied by airway hyperreactivity. [1]

Tobacco smoking is the major cause of COPD, so cessation of smoking is important in the prevention and treatment of COPD. Current therapy (e.g., bronchodilators) treats the symptoms of COPD and not the actual condition.

The rationale for the use of PDE₄ inhibitors in the treatment of COPD is based upon the role of cyclic adenosine monophosphate (cyclic AMP) as a second messenger that mediates a broad suppression of immune and inflammatory cell activity. SB 207499 has been shown to have marked anti-inflammatory and bronchodilatory activity in multiple *in vitro* and *in vivo* settings. Consequently, PDE₄ inhibitors such as SB 207499 could represent important new treatments for COPD.

In support of the asthma and COPD clinical programs, 13 Phase I studies have been completed to characterise the safety, tolerability, pharmacokinetics and potential drug interaction profile of SB 207499. A total of 1547 patients have been enrolled into eight Phase II clinical trials designed to explore the safety and efficacy of a range of doses of SB 207499. Six studies were conducted in asthmatic patient populations and two studies in patients with COPD.

The Phase II COPD clinical program consisted of studies 032 and 038, conducted in Europe and the US, respectively. The study design and entry criteria for both studies were standardised. COPD was defined by International Treatment Guidelines and entry criteria were established to ensure that patients had COPD rather than asthma. Both studies 032 and 038 were multicentre, double-blind, placebo-controlled, dose-ranging trials. Study 032 was of six weeks duration and evaluated SB 207499 dosages of 5, 10 and 15 mg bid. Study 038 investigated lower doses of 2.5 and 5 mg bid for four weeks. In both studies, the primary efficacy endpoint was clinic trough FEV₁. The results of study 032 demonstrated significant and clinically relevant

efficacy of SB 207499 at 15 mg bid. SB 207499 15 mg bid was significantly superior to placebo with respect to improvements in pulmonary function parameters (FEV₁, FVC and PEF_R). Superiority was substantiated by positive trends in symptoms (dyspnoea) and a reduction in beta₂-agonist use.

Administration of SB 207499 to healthy volunteers at dosages up to and including 15 mg bid has been well tolerated and has not raised any safety concerns. Adverse experiences in the Phase I studies have, in general, been mild to moderate, with nausea and headache as the most commonly reported events. SB 207499 (repeat dosing up to 15 mg bid) was generally well tolerated in the Phase II program. There is no evidence of any adverse effect on laboratory parameters, vital sign values, or electrocardiographic parameters. Headache and nausea were the adverse experiences most commonly associated with treatment with SB 207499, though these events tended to be mild, and infrequently led to withdrawal. The gastrointestinal adverse experiences typically occurred early during treatment, resolved on therapy during the study, and tended not to recur.

The Phase III COPD program consists of three 6-month randomised, double-blind efficacy and safety trials. Patients completing these studies will have the option of receiving open label medication with SB 207499 (15 mg bid) in one of two extension studies (studies 040 – Europe, South Africa and Australia/New Zealand and 041 – US and Canada). The present study, study 040, is intended to evaluate the long-term safety of SB 207499 (15 mg bid) and to explore the long term efficacy of the compound. Prior to enrolment in study 040, patients must have completed study 042 or study 091 where patients received SB 207499 15 mg bid or placebo for 24 weeks in study 042 and 26 weeks in study 091.

2.0 Objectives

2.1 Primary Objective

The primary objective of this study is to evaluate the long-term safety and tolerability of SB 207499 administered at a dosage of 15 mg bid in patients with COPD.

2.2 Secondary Objective

The secondary objective of this study is to evaluate further the efficacy of SB 207499 in terms of pulmonary function, disease symptoms and quality of life.

3.0 Study Design Overview and Flow Chart

This is a multicentre, Phase III, open-label extension study in patients with COPD. The study will continue until the compound is registered or the project is terminated by the sponsor.

Patients who have previously completed study 042 or study 091 must satisfy additional inclusion and exclusion criteria ([Sections 4.2](#) and [4.3](#)) before beginning Protocol 040 at a dosage of SB 207499 of 15 mg bid. Patients will be assessed for their eligibility for study 040 at their final scheduled visit of study 042 at Week 24, or study 091 at Week 26 (i.e. prior to Safety Follow-up visit). The study blind from the previous studies will not be broken before entering into study 040.

During the treatment period, patients will attend the clinic after one, two, and four weeks and then at four-week intervals until at least Week 48, followed by 12-weekly visits until the end of the study ([Figure 1](#)).

The transition of patients from 4-weekly to 12-weekly visits should be performed as follows:

Patients should continue with 4-weekly visits until their next visit which is a multiple of 12 weeks since Week 0 in study 040 (i.e. Week 48, 60, 72, 84 or 96), after which visits will be scheduled at 12-weekly intervals. In this way, all continuing patients will complete a visit at Weeks 48, 60, 72 etc. E.g. A patient who has just attended a visit at Week 52 must attend at Week 56 and Week 60, before switching to 12-weekly visits (Week 72, Week 84 etc.).

The assessments specified in [Table 1](#) and in [Section 5.3](#) will be made. Patients will return for a follow-up visit one to two weeks after the last visit on open-label treatment.

On non-visit days, study medication will be taken orally, twice daily, in the morning *after* breakfast and in the evening *after* a meal. **Note:** Patients entering study 040 from study 042 will take the final dose of study 042 medication in clinic prior to entering study 040 and will take first dose of 040 study medication after their evening meal allowing at least 8 hours since the time of the last dose of study medication taken in the clinic. On visit days, patients will refrain from taking the morning dose of study medication before their clinic visit.

All other COPD medications (with the exception of theophylline and aminophylline (oral and intravenous)) will be permitted without restriction for all patients in Protocol 040.

Figure 1: Study Design

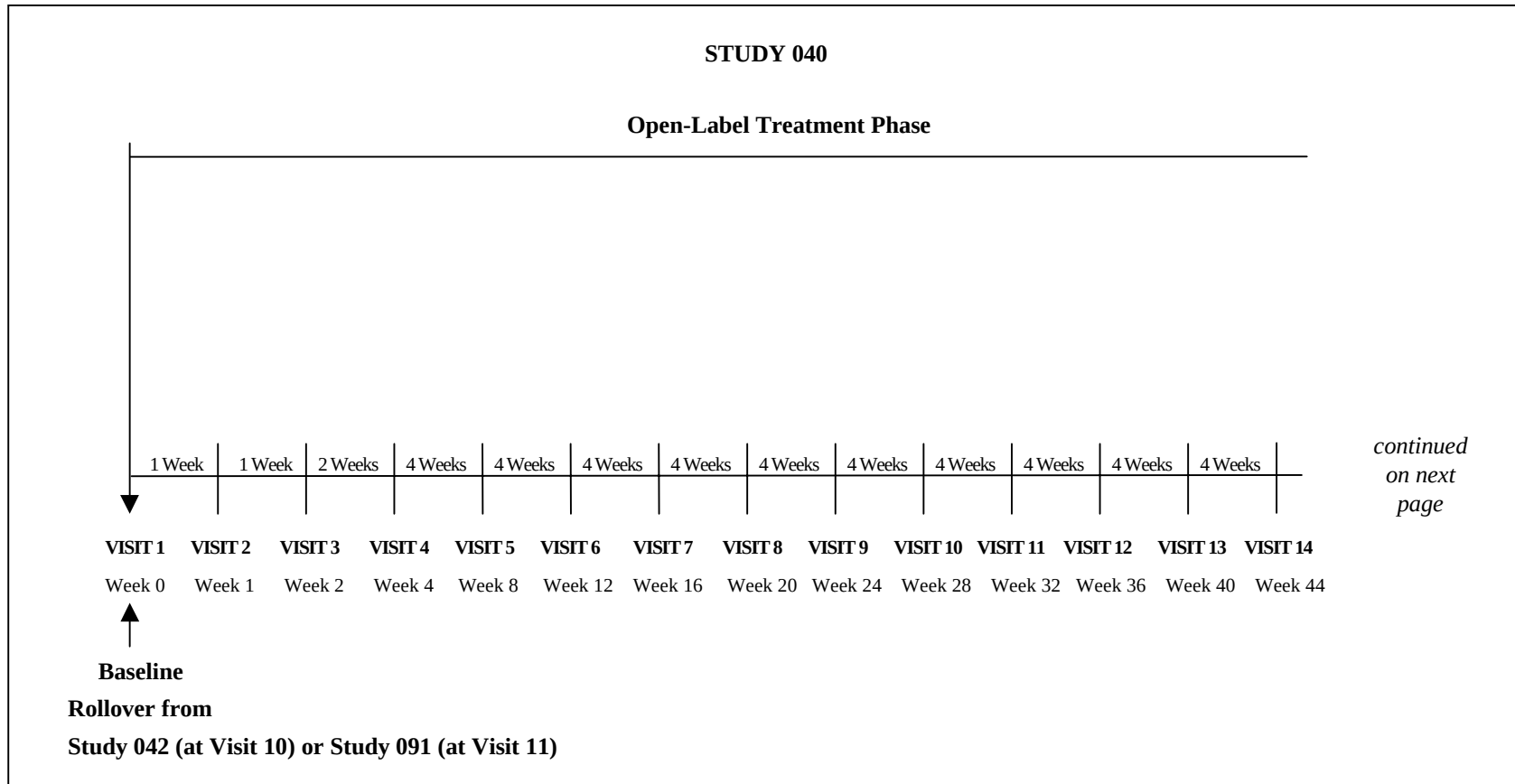


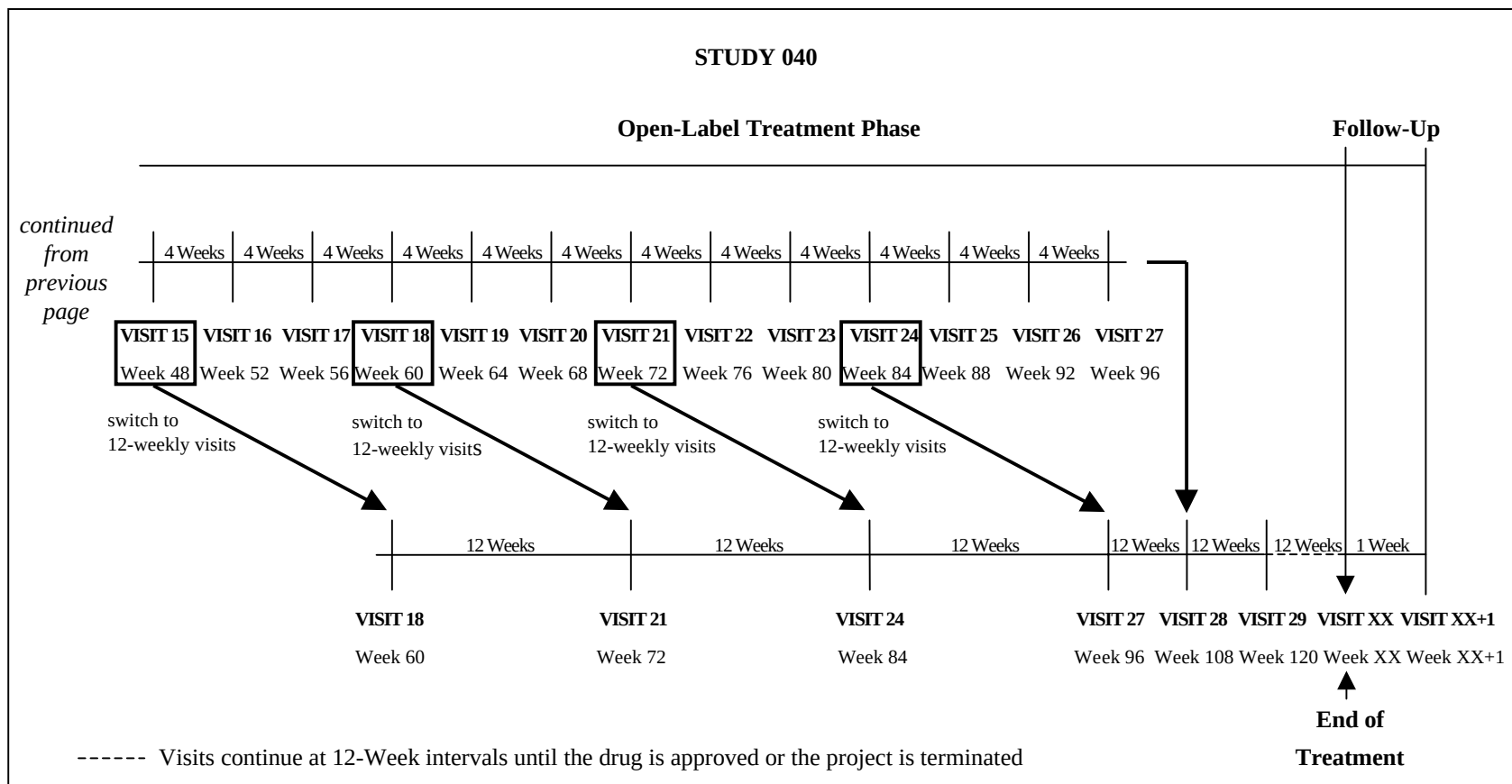
Figure 1: Study Design (Continued)

Table 1: Outline of Study Procedures

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15		
Time relative to baseline (weeks)	Baseline 0	+1	+2	4	8	12	16	20	24	28	32	36	40	44	48	Early Withdrawal	Follow-up Final Visit +1 week
Signed written informed consent	x																
Study medication compliance		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant medication	x ¹	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Diary card review ⁷		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse experiences ⁸	x ¹	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
COPD exacerbation assessment/ healthcare utilisation	x ¹	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical (including respiratory) examination	x ¹								x						x	x	x ²
Resting 12-lead ECG	x ¹	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x ²
Vital signs (BP, HR) ³	x ¹	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Overall Breathlessness (modified Borg)	x ¹		x	x	x	x	x	x	x	x	x	x	x	x	x		
Exercise tolerance test (6-minute walk)	x ¹					x			x			x			x		
Post-exercise breathlessness	x ¹					x			x			x			x		
Pulmonary function tests ⁴	x ¹		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Laboratory tests ⁵	x ¹	x	x	x	x	x	x	x	x ⁵	x	x	x	x	x	x ⁵	x	x ²
Pregnancy test ⁶	x ¹			x	x	x	x	x	x	x	x	x	x	x	x	x	x
Quality of life assessments: SGRQ	x ¹					x			x						x	x	
Quality of life assessments: SF-36	x ¹								x						x	x	
Dispense or re-dispense open-label medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Study conclusion record																x	

Continued

Table 1: Outline of Study Procedures (Continued)

Visit	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	Early Withdrawal	Follow-up Final Visit +1 week
Time relative to baseline (weeks)	52*	56*	60	64*	68*	72	76*	80*	84	88*	92*	96	108	120	132	144	156		
Study medication compliance	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Diary card review ⁷	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse experiences ⁸	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
COPD exacerbation assessment/ healthcare utilisation	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical (including respiratory) examination						x						x		x		x**		x	x ²
Resting 12-lead ECG	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x ²
Vital signs (BP, HR) ³	x	x	x	x	x	x	x	x	x	x	x	x ³	x	x	x	x ³	x	x ³	x
Overall Breathlessness (modified Borg)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Exercise tolerance test (6-minute walk)			x			x			x			x	x	x	x	x	x		
Post-exercise breathlessness			x			x			x			x	x	x	x	x	x		
Pulmonary function tests ⁴	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Laboratory tests ⁵	x	x	x	x	x	x	x	x	x	x	x	x ⁵	x	x	x	x ⁵	x	x ⁵	x ²
Pregnancy test ⁶	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Quality of life assessments: SGRQ						x						x		x		x**		x	
Quality of life assessments: SF-36						x						x		x		x**		x	
Dispense or re-dispense open-label medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Study conclusion record																		x	

- 1 Assessed during Visit 10, final double-blind visit, of Study 042 and visit 11 of Study 91 (except the QoL assessments for study 091 which are performed at visit 10)
- 2 Only if abnormalities are present at the previous visit
- 3 Orthostatic blood pressure and heart rate are measured at 24 weeks, 48 weeks and 48-weekly thereafter. Also at Early Withdrawal
- 4 To include FEV₁, FEV₆, FVC, FEF₂₅₋₇₅, FEF₇₅, and PEF_R
- 5 Faecal occult blood is measured at 24 weeks, 48 weeks and 48-weekly thereafter. Also at Early Withdrawal. Baseline measure is taken from last FOB in study 042 or study 091.
- 6 Serum pregnancy test for female patients of child bearing potential. Urine test only is done at Follow-up Visit.
- 7 A Diary Card is issued at each visit. The patient will use the Diary Card to record if they feel differently since the previous visit
- 8 Patients will be assessed for GI AEs at every visit
- * Visit not to be performed once patient has switched to 12-weekly visits.
- ** Measured every 24 weeks thereafter

4.0 Study Population

4.1 Number of Patients

It is anticipated that approximately 600 patients will be entered in the study. Approximately 200 centres within Europe, South Africa and Australia/New Zealand are to participate.

4.2 Inclusion Criteria

Patients who fulfil the following criteria will be eligible for inclusion in the study.

- 1 Males or females with COPD who have successfully completed study 042 or study 091 where patients received SB 207499 15 mg bid or placebo for 24 weeks in study 042 and 26 weeks in study 091 without tolerability problems.

Note: Women of childbearing potential must be using effective contraceptive measures (i.e., oral contraceptives, Norplant[®], an IUD, a diaphragm with spermicide, a condom with spermicide, or Depo-Provera[®]) prior to Visit 1 and must continue using the same contraceptive measure during the study.

- 2 Patients who have given their written informed consent to participate.

4.3 Exclusion Criteria

The following patients are not eligible for inclusion into the study.

- 1 Women who are pregnant or lactating, or who plan for pregnancy within the next 24 months
- 2 Patients who withdrew from study 042 or study 091 for any reason
- 3 Patients with a positive faecal occult blood test between Weeks 20 and 24 in study 042 and study 091
- 4 Patients who experienced a serious adverse experience, a gastrointestinal adverse experience or a clinically significant laboratory abnormality, which in the opinion of the Investigator could have been attributed to study medication, during study 042 or study 091 and which was still present at the end of either study.

- 5 Patients who in the opinion of the Investigator are not suitable for enrolment into the study.

5.0 Conduct of the Study

5.1 Ethics and Regulatory Considerations

The study will be conducted according to Good Clinical Practice, the World Medical Association Declaration of Helsinki ([Appendix A](#)).

5.1.1 Ethics Review Committee/Institutional Review Board

Ethics Review Committees (ERCs)/Institutional Review Boards (IRBs) must be constituted according to the local laws/customs of each participating country.

This protocol will be submitted to an appropriate committee or board and its written unconditional approval obtained and submitted to the sponsor before the study is begun. SmithKline Beecham (SB) will supply the Investigator with relevant data for submission to the hospital/university/independent ERC/IRB for the review and approval of the protocol. Verification of the ERC/IRB's unconditional approval of the protocol and the written informed consent statement will be transmitted to the SB study monitor prior to shipment of drug supplies and case report forms (CRFs) to the site. This approval must refer to the study by exact protocol title and number, identify the documents reviewed, and state the date of review.

The ERC/IRB must be informed by the Investigator of all subsequent protocol amendments and of serious or unexpected adverse experiences occurring during the study that are likely to affect the safety of the subjects or the conduct of the study. Approval for such changes must be transmitted in writing to the SB study monitor via the Investigator.

5.1.2 Informed Consent

The principles of informed consent in the current edition of the World Medical Association Declaration of Helsinki ([Appendix A](#)) should be implemented in each clinical study before protocol-specified procedures are carried out.

Information should be given in both oral and written form whenever possible and deemed appropriate by the ERC/IRB. Subjects and their relatives, guardians, or if necessary, legal representatives must be given ample opportunity to inquire about details of the study.

The consent form generated by the Investigator with the assistance of SB, must be approved (along with the protocol) by the ERC/IRB and be acceptable to SB. Consent forms must be in a language fully comprehensible to the prospective subject. Where appropriate, informed consent shall be documented by the use of a written consent form approved by the ERC/IRB and signed by the subject or the subject's legally authorised representative. The written consent document will embody the elements of informed consent as described in the World Medical Association Declaration of Helsinki and will also comply with local regulations. This form may be read to the subject or the subject's legally authorised representative, but, in any event, the Investigator shall give either the subject or the representative adequate opportunity to read it before it is signed.

Consent must be documented either by the subject's dated signature or by the signature of an independent witness who records the subject's assent. In either event, the signature confirms that the consent is based on information that has been understood. Each subject's signed informed consent form must be kept on file by the Investigator for possible inspection by regulatory authorities and/or SB professional and regulatory compliance personnel.

A sample informed consent is provided in [Appendix C](#).

5.2 General Instructions

5.2.1 Study Visits

For each scheduled study visit, patients will be required to attend the clinic in the morning, at about the same time of day (preferably 10:00 ± 2 hours), not having taken the morning dose of study medication, and having refrained from using beta₂-agonists (short-acting), anticholinergic medications and smoking during the two-hour period and from using beta₂-agonists (long-acting) during the 12-hour period preceding the visit.

Smoking and the use of beta₂-agonists or anticholinergic treatment must be avoided during the clinic stay if at all possible. Patients must **not** take their morning doses of study medication before attending morning clinic visits.

In exceptional circumstances, a patient may be allowed afternoon appointments only if **≥ 8 hours have elapsed** since the last dose of study medication and the Investigator is capable of completing all visit assessments. This will ensure that trough measurements are obtained. For example, if the morning dose of study medication is taken after breakfast at 8:00 a.m., the patient's appointment may be scheduled after 4:00 p.m. the same day. If an afternoon visit is scheduled, patients

should be instructed to take the morning dose of study medication after breakfast, which must be at least 8 hours before their clinic visit.

5.2.2 Assignment of Patient Identification Numbers

The patient number assigned to each patient during study 042 or study 091 will be used for that patient during Protocol 040.

5.3 Study Sequence

Patients completing study 042 or study 091 will enter study 040 at their final "On-therapy" visit (i.e. Visit 10 for study 042 and Visit 11 for study 091). **There should be no gap between completing the preceding study and entering study 040.**

5.3.1 Week 0, Visit 1

Data from Visit 10 (Week 24) of study 042 or Visit 11 (week 26) of study 091 will provide the Visit 1 data, including:

- Quality of life assessments – SGRQ and SF-36 ([Section 7.3](#)). (This assessment is performed at visit 10 for patients in study 091.)
- Concomitant medication
- Adverse experiences
- COPD exacerbation assessment and healthcare utilisation assessment ([Sections 7.1, 7.2](#) and [8.1.1](#))
- Physical examination, including a respiratory examination ([Section 5.4.1](#))
- Smoking status and Pulmonary Rehabilitation Programme status
- Sitting blood pressure and heart rate; orthostatic blood pressure and heart rate ([Section 5.4.1](#))
- Resting 12-lead ECG ([Section 5.4.2](#))
- Blood and urine samples for routine haematology, biochemistry and urinalysis (pregnancy testing for females of childbearing potential) ([Section 5.4.3](#))
- Pulmonary function tests ([Section 5.4.5](#))
- Exercise tolerance test (6-minute walk test) ([Section 5.4.6](#)).

- Overall breathlessness assessment (Borg scale) ([Section 5.4.7](#))
- Post-exercise breathlessness ([Section 5.4.7](#))

Note: Any assessments that were not performed at the Visit 10 or Visit 11 of study 042 and 091, will be performed at this visit.

A checklist of the inclusion and exclusion criteria ([Sections 4.2](#) and [4.3](#)) will be completed and written informed consent obtained. If the patient is eligible to enter study 040, the patient's identification number (PID) from study 042 or study 091 will be copied onto the CRF and the following should be performed:

- Issue one bottle (a 35-day supply) of open-label study medication.

Patients entering study 040 from study 091 will take the first dose from the new bottle of study medication in the clinic with food, and patients will be reminded to take the first evening dose of medication after their evening meal (at approximately 20:00).

Patients entering study 040 from study 042 will take the first dose from the new bottle of study medication after their evening meal allowing at least 8 hours since the time of the last dose of study medication taken in the clinic.

- Issue a diary card which will be used by the patient to record if they feel differently since starting the study. A diary card will be issued at each visit.
- Review the procedure for reporting gastrointestinal adverse experiences with the patient ([Section 8.1.2](#)).

Patients will be instructed to return to the clinic within 7 (± 2) days for the Week 1 visit (Visit 2) and reminded:

- Not to take the morning dose of SB 207499 on the morning of the Week 1 visit (Visit 2) if a morning appointment is scheduled
- To refrain from taking beta₂-agonists (short-acting) or anticholinergic medications for two hours and beta₂-agonist (long-acting) for 12 hours before the next visit.
- To refrain from smoking for two hours immediately preceding the Week 1 visit (Visit 2)
- To bring all empty medication bottles and any remaining study medication to the next clinic visit.

5.3.2 End of Week 1 (Visit 2)

At the end of Week 1, the following procedures will be completed:

- Document if the patient has taken inhaled beta₂-agonists (short-acting), anticholinergic medication, or smoked during the two-hour period or beta₂-agonists (long-acting) during the 12-hour period preceding the visit.
- The diary card will be collected and reviewed ([Section 5.4.4](#)). Any adverse experiences which have occurred will be recorded in the CRF and followed-up as necessary ([Section 8.0](#)).
- Compliance in taking study medication will be determined ([Section 6.9](#)). The Investigator will emphasise the importance of compliance to patients with compliance <80% or >120%.
- Any changes or additions to the patient's concomitant medication and any additions to medical procedures will be recorded in the CRF ([Section 6.4](#)). Smoking status will also be documented.
- Determine if the patient has entered a Pulmonary Rehabilitation Programme since the last visit.
- A COPD exacerbation assessment will be made to determine if the patient has experienced any exacerbations since the last visit ([Section 8.1.1](#)).
- A healthcare utilisation assessment will be performed ([Sections 7.1](#) and [7.2](#)).
- Blood and urine samples will be obtained for routine haematology, biochemistry and urinalysis ([Section 5.4.3](#)).

Greater than 2 hours after the patient's last short-acting beta₂-agonist or greater than 12 hours after the last long-acting beta₂-agonist:

- A 12-lead electrocardiogram will be performed after the patient has been semisupine for 5 minutes ([Section 5.4.2](#)).
- Blood pressure and heart rate will be measured after 5 minutes in a sitting position ([Section 5.4.1](#)).

Patients who withdraw from the study during the visit should complete all scheduled visit assessments along with pulmonary function tests, the SGRQ and SF-36 questionnaires, a physical examination, assessments of orthostatic changes in blood pressure and heart rate and faecal occult blood ([Section 5.3.8](#)).

For patients continuing in the study:

- **Reissue the bottle of study medication dispensed at Visit 1.** The next dose of study medication will be administered in the clinic with food.
- Issue a new diary card. The patient should be reminded to use the card to record if they feel differently since starting the study.
- Review reporting requirements for gastrointestinal symptoms ([Section 8.1.2](#)).

Patients will be instructed to return to the clinic for the Week 2 visit (Visit 3) in 7 (± 2) days. Patients will also be reminded:

- to take the evening dose immediately after the evening meal.
- **not** to take the morning dose of study medication at home on the morning of the next clinic visit if a morning appointment is scheduled.
- to refrain from taking beta₂-agonists (short-acting) or anticholinergic medications for two hours and beta₂-agonists (long-acting) for 12 hours before the next visit.
- to refrain from smoking for two hours immediately preceding the next visit.
- to bring any remaining study medication tablets, all study medication containers, and diary card with them to the next visit.

5.3.3 End of Week 2 (Visit 3)

At the end of Week 2, the following procedures will be completed:

- Document if the patient has taken inhaled beta₂-agonists (short-acting), anticholinergic medication, or smoked during the two-hour period or beta₂-agonists (long-acting) during the 12-hour period preceding the visit.
- The diary card will be collected and reviewed ([Section 5.4.4](#)). Any adverse experiences which have occurred will be recorded in the CRF and followed-up as necessary ([Section 8.0](#)).
- Compliance in taking study medication will be determined ([Section 6.9](#)).
- Any changes or additions to the patient's concomitant medication and any additional medical procedures will be recorded in the CRF ([Section 6.4](#)). Any changes in smoking status will also be documented.

- Determine if the patient has entered a Pulmonary Rehabilitation Programme since the last visit.
- A COPD exacerbation assessment will be made to determine if the patient has experienced any exacerbations since the last visit ([Section 8.1.1](#)).
- A healthcare utilisation assessment will be performed ([Sections 7.1](#) and [7.2](#)).
- Overall breathlessness will be assessed using the modified Borg scale ([Section 5.4.7](#)).

To continue in the study, patients must show **>80% or < 120%** compliance in taking study medication at two consecutive visits. Patients who do not meet this criterion must be withdrawn from the study.

The following assessments will be made:

- Blood and urine samples will be obtained for routine haematology, biochemistry and urinalysis ([Section 5.4.3](#)).

Greater than 2 hours after the patient's last short-acting beta2-agonist or greater than 12 hours after the last long-acting beta2-agonist:

- A 12-lead electrocardiogram will be performed after the patient has been semisupine for 5 minutes ([Section 5.4.2](#)).
- Blood pressure and heart rate will be measured after 5 minutes in a sitting position ([Section 5.4.1](#)).
- Pulmonary function tests will be performed before administration of the next dose of study medication in the clinic ([Section 5.4.5](#)). **Note: If the patient has taken short acting beta2-agonists or anticholinergic medication during the 2 hours prior to the visit, a 2-hour period should elapse before pulmonary function tests are performed. If the patient has taken long-acting beta2-agonists during the 12 hours prior to the visit, a total of 12 hours must elapse before pulmonary function tests are performed.**

Patients who withdraw from the study during the visit should complete all scheduled visit assessments, the SGRQ and SF-36 questionnaires, a physical examination, assessments of orthostatic changes in blood pressure and heart rate and faecal occult blood ([Section 5.3.8](#)).

For patients who are continuing in the study:

- **Reissue the bottle of study medication dispensed at Visit 1.** The next morning dose of study medication will be administered in the clinic with food.
- Issue a new diary card. The patient should be reminded to use the card to record if they feel differently since starting the study.
- Review the procedure for reporting gastrointestinal adverse experiences with the patient.

Patients will be asked to return to the clinic in the morning in 14 ($\pm$ 3) days for the Week 4 visit (Visit 4). They will also be reminded:

- to take the next dose immediately after the evening meal.
- **not** to take the morning dose of study medication at home on the morning of their next clinic visit if a morning appointment is scheduled.
- To refrain from taking beta₂-agonists (short-acting) or anticholinergic medications for two hours and beta₂-agonists (long-acting) for 12 hours before the next visit.
- to refrain from smoking for 2 hours immediately preceding the next visit.
- to bring any remaining study medication tablets, all study medication containers, and the diary card with them to the next visit.

5.3.4 Visits at 4-Week Intervals (Weeks 4, 8, 12, 16, 20, 24, 28, etc; Visits 4, 5, 6, 7, 8, 9, 10, etc.)

At the end of every 4-week interval (until the patient commences 12-weekly visits, see [Section 5.3.5](#)), the following will be performed:

- Document if the patient has taken inhaled beta₂-agonists (short-acting), anticholinergic medication, or smoked during the two-hour period or beta₂-agonists (long-acting) during the 12-hour period preceding the visit.
- The diary card will be collected and reviewed ([Section 5.4.4](#)). Any adverse experiences which have occurred will be recorded in the CRF and followed-up as necessary ([Section 8.0](#)).
- Compliance in taking study medication will be determined ([Section 6.9](#)). Any medication remaining in the returned bottle will be retained by the Investigator.

- Any changes or additions to the patient's concomitant medication and any additions to medical procedures will be recorded in the CRF ([Section 6.4](#)). Smoking status will also be documented.
- Determine if the patient has entered a Pulmonary Rehabilitation Program since the last visit.
- A COPD exacerbation assessment will be made to determine if the patient has experienced any exacerbations since the last visit ([Section 8.1.1](#)).
- A healthcare utilisation assessment will be performed ([Sections 7.1](#) and [7.2](#)).
- Overall breathlessness will be assessed using the modified Borg scale ([Section 5.4.7](#)).

To continue in the study, patients must show > **80% or** < **120%** compliance in taking study medication at two consecutive visits. Patients who do not meet this criterion must be withdrawn from the study.

The following assessments will be made:

- Blood and urine samples will be obtained for routine haematology, biochemistry (including beta-HCG for women of childbearing potential) and urinalysis ([Section 5.4.3](#)).

Greater than 2 hours after the patient's last short-acting beta2-agonist or greater than 12 hours after the last long-acting beta2-agonist:

- A 12-lead electrocardiogram will be performed after the patient has been semisupine for 5 minutes ([Section 5.4.2](#)).
- Blood pressure and heart rate will be measured after 5 minutes in a sitting position ([Section 5.4.1](#)).
- Pulmonary function tests will be performed before administration of the next dose of study medication in the clinic ([Section 5.4.5](#)). **Note: If the patient has taken short acting beta2-agonists or anticholinergic medication during the 2 hours prior to the visit, a 2-hour period should elapse before pulmonary function tests are performed. If the patient has taken long-acting beta2-agonists during the 12 hours prior to the visit, a total of 12 hours must elapse before pulmonary function tests are performed.**

Patients who withdraw from the study during the visit should complete all scheduled visit assessments. In addition, the SGRQ and SF-36 questionnaires, a physical examination, assessments of orthostatic changes in blood pressure and

heart rate and faecal occult blood tests should be completed if not performed at that visit ([Section 5.3.8](#)).

For patients who are continuing in the study:

- Issue one bottle (a 35-day supply) of study medication. The next morning dose of study medication will be administered in the clinic with food.
- A new diary card will be issued. The patient will be reminded to use the card to record if they feel differently since starting the study.
- Review the procedure for reporting gastrointestinal adverse experiences with the patient.

Patients will be asked to return to the clinic at the same time of day in 28 ($\pm$ 6) days for their next visit. They will also be reminded:

- to take the next dose immediately after the evening meal.
- **not** to take the morning dose of study medication at home on the day of their next clinic visit if a morning appointment is scheduled.
- to refrain from taking beta₂-agonists (short-acting) or anticholinergic medications for two hours and beta₂-agonists (long-acting) for 12 hours immediately preceding the next visit.
- to refrain from smoking for 2 hours immediately preceding the next visit.
- to bring with them any remaining study medication tablets, all study medication containers, and the diary cards.

5.3.5 Visits at 12-Week Intervals (Weeks 12, 24, 36, 48, 60, 72, 84, 96 etc.; Visits 6, 9, 12, 15, 18, 21, 24, 27 etc.)

In addition to the procedures which will be performed at 4-week intervals ([Section 5.3.4](#)), the following assessments will occur at 12-week intervals. Once patients commence 12-weekly visits, the following assessments, and all those described for 4-week intervals, will be performed at each visit.

Greater than 2 hours after the patient's last short-acting beta₂-agonist or greater than 12 hours after the last long-acting beta₂-agonist:

- An exercise tolerance test (6-minute walk) will be completed ([Section 5.4.6](#)).
- Breathlessness using the modified Borg scale, will be assessed immediately after the exercise tolerance test ([Section 5.4.7](#)).

Note: At least 10 minutes should elapse between the exercise tolerance test and pulmonary function testing so that the patient is fully rested during their pulmonary function tests.

For patients attending visits at 12-weekly intervals:

- Issue a 105- day supply of study medication: either three bottles containing 70 tablets, or one bottle containing 210 tablets.

Patients will be asked to return to the clinic at the same time of day in 84 (± 6) days for their next visit.

5.3.6 Visits at 24-Week Intervals (Weeks 24, 48, 72, 96 etc.; Visits 9, 15, 21, 27 etc.)

At the end of Weeks 24, 48, 72 and 96, and each subsequent 24-week interval, the assessments described for the 4- and 12 -week intervals will be performed ([Sections 5.3.4](#) and [5.3.5](#)). The following evaluations will also be performed:

- Quality of life questionnaires, the SGRQ and the SF-36, will be administered before any other assessments ([Section 7.3](#), [Appendices E](#) and [F](#)).
- Physical examination, including respiratory examination ([Section 5.4.1](#)).
- Orthostatic blood pressure and heart rate will be measured after 5 minutes in a supine position followed by sitting with legs dependent for 1 minute ([Section 5.4.1](#)). **Orthostatic measures will be made at 24 weeks and 48 weeks and 48-weekly thereafter.**
- Patients will be issued a faecal occult blood kit and instructed to follow the instructions on the kit ([Section 5.4.3](#)). **Faecal occult blood will be assessed at 24 weeks and 48 weeks and 48-weekly thereafter.**

All of these assessments will be performed at the last on-therapy visit for all patients.

5.3.7 Safety Follow-up Visit

A Follow-up visit will be required one week after the last visit on open-label treatment. At this visit, the Investigator will:

- Document if the patient has taken inhaled beta₂-agonists (short-acting), anticholinergic medication, or smoked during the two-hour period or beta₂-agonists (long-acting) during the 12-hour period preceding the visit.

- Record in the CRF and follow up, as appropriate, any adverse experiences that have occurred ([Section 8.0](#))
- Record in the CRF any changes or additions to patient's concomitant medications and any additional medical procedures. Smoking status will also be documented.
- Determine if the patient has entered a Pulmonary Rehabilitation Program since the last visit.
- Perform a COPD exacerbation assessment and healthcare utilisation assessment (Sections [7.1](#), [7.2](#) and [8.1.1](#)).

The following assessments will also be made:

- A physical examination, including a respiratory examination, will be performed if abnormal findings were observed at the last visit ([Section 5.4.1](#))
- Blood and urine samples will be obtained for routine haematology and biochemistry and urinalysis only if abnormal findings were observed at the last visit ([Section 5.4.3](#))
- A urine pregnancy test will be performed for all women of child-bearing potential ([Section 5.4.3](#)).

Greater than 2 hours after the patient's last short-acting beta₂-agonist or greater than 12 hours after the last long-acting beta₂-agonist:

- Sitting blood pressure and heart rate ([Section 5.4.1](#))
- A 12-lead electrocardiogram will be performed after the patient has been semisupine for 5 minutes if abnormal findings were observed at the last visit ([Section 5.4.2](#))
- Pulmonary function tests ([Section 5.4.5](#)). **Note: If the patient has taken short acting beta₂-agonists or anticholinergic medication during the 2 hours prior to the visit, a 2-hour period should elapse before pulmonary function tests are performed. If the patient has taken long-acting beta₂-agonists during the 12 hours prior to the visit, a total of 12 hours must elapse before pulmonary function tests are performed.**

5.3.8 Early Withdrawal

Early withdrawal assessments and procedures should be completed for all patients who withdraw or are withdrawn from the study after receiving open-label treatment, but prior to the end of the open-label treatment phase. For patients who withdraw or are withdrawn at a scheduled visit, the assessments and procedures will be performed at that visit. Patients who withdraw or are withdrawn between scheduled visits should have an early withdrawal visit scheduled within 24 hours after discontinuation of study medication. If patients are unable to return within 24 hours they will be asked to return in 7 ($\pm$ 3) days for a safety follow-up visit. The following assessments and procedures will be performed at the early withdrawal visit:

- Quality of life questionnaires, the SGRQ and the SF-36, will be administered before any other assessments ([Section 7.3](#), Appendices E and F)
- Review patient diary ([Section 5.4.4](#)) and record in the CRF and follow up, as appropriate, any adverse experiences that have occurred ([Section 8.0](#))
- Compliance in taking study medication will be determined ([Section 6.9](#)).
- Record in the CRF any changes or additions to patient's concomitant medications and any additional medical procedures. Smoking status will also be documented.
- Determine if the patient has entered a Pulmonary Rehabilitation Program since the last visit.
- Perform a COPD exacerbation assessment and healthcare utilisation assessment (Sections [7.1](#), [7.2](#) and [8.1.1](#))
- Physical examination, including a respiratory examination ([Section 5.4.1](#))
- Blood and urine samples for routine haematology, biochemistry and urinalysis (pregnancy testing for females of childbearing potential) ([Section 5.4.3](#))
- Patients will be issued faecal occult blood kit ([Section 5.4.3](#))

Greater than 2 hours after the patient's last short-acting beta2-agonist or greater than 12 hours after the last long-acting beta2-agonist:

- Sitting blood pressure and heart rate; orthostatic blood pressure and heart rate ([Section 5.4.1](#))
- Resting 12-lead ECG ([Section 5.4.2](#))

- Pulmonary function tests ([Section 5.4.5](#)). **Note: If the patient has taken short acting beta2-agonists or anticholinergic medication during the 2 hours prior to the visit, a 2-hour period should elapse before pulmonary function tests are performed. If the patient has taken long-acting beta2-agonists during the 12 hours prior to the visit, a total of 12 hours must elapse before pulmonary function tests are performed.**
- Study conclusion record.

5.4 Clinical Observations and Procedures

5.4.1 Physical Examination and Respiratory Examination (24-week Intervals) and Vital Signs (All Visits)

At each 24-week interval, at early withdrawal and at the Follow-up visit (if abnormal at the previous visit), the Investigator will answer the following question "Has there been a clinically significant worsening since the last assessment in the patient's physical condition?" A specific respiratory examination will also be made. All significant findings will be recorded in the CRF.

Greater than 2 hours after the patient's last short-acting beta2-agonist or greater than 12 hours after the last long-acting beta2-agonist administration, vital signs (blood pressure and heart rate) will be measured at all visits after the patient has been sitting for at least five minutes.

At Weeks 24, 48 and annually thereafter; at early withdrawal and at visits associated with gastrointestinal adverse experiences, orthostatic heart rate and blood pressure will be obtained after the patient has been supine for 5 minutes and then after the patient sits up with legs dependent for 1 minute.

At visits required within 24 hours of the occurrence of gastrointestinal adverse experiences ([Section 8.1.2](#)), a structured assessment of these adverse experiences including a physical examination will be performed as detailed in [Appendix F](#).

5.4.2 Electrocardiograph (ECG) (All Visits)

Greater than 2 hours after the patient's last short-acting beta2-agonist or greater than 12 hours after the last long-acting beta2-agonist administration, a 12-lead ECG will be performed at all visits including Follow-up (if abnormal at the previous visit) or upon early withdrawal after the patient has been semisupine for 5 minutes. Each ECG recording will be clearly labelled with patient initials, patient identification number, protocol number, centre number and date performed. The ECGs will be reviewed by the Investigator for clinically

significant abnormalities. ECGs will be transferred to a centralised facility for data processing.

5.4.3 Laboratory Tests (All Visits)

Approximately 20 ml of blood will be collected for laboratory analyses at each visit and at early withdrawal. Blood and urine samples will be collected at the Follow-up Visit, only if abnormalities were observed at the previous visit. A urine pregnancy test will always be performed at the Follow-up Visit for women of child-bearing potential.

The following parameters will be measured:

Haematology: Haemoglobin concentration, haematocrit, red cell count, white cell count with differential, platelet count

Clinical chemistry: Blood urea, creatinine, aspartate transaminase (ASAT/SGOT), alanine transaminase (ALAT/SGPT), gamma glutamyl-transferase (GGT), alkaline phosphatase (ALP), total protein, albumin, total bilirubin, sodium, potassium, chloride, glucose, uric acid.

Amylase will be measured for patients who report gastrointestinal symptoms which are of concern to them or interfere with daily activities (see [Section 8.1.2](#)).

Faeces: Faecal occult blood tests will be performed at Weeks 24, 48 and annually thereafter, and at early withdrawal. Three tests collected on consecutive bowel movements, if possible, are to be performed according to the instructions provided with the faecal occult blood kits. In particular, patients are not to collect samples during or until 3 days after a menstrual period or while they have bleeding haemorrhoids or blood in the urine. In addition, patients are to avoid aspirin or other non-steroidal anti-inflammatory drugs for 7 days prior to and during the test period and to avoid Vitamin C in excess of 250 mg per day from all sources, red meat including processed meats and liver, and raw fruits and vegetables for 72 hours prior to and during the test period. When the samples are returned for analysis, the Investigator will question the patient to determine whether the instructions were followed.

Faecal occult blood will also be tested in patients who report gastrointestinal symptoms that are of concern to them or interfere with daily activities (see [Section 8.1.2](#)). When the samples are returned for analysis, the Investigator will question the patient to determine if the results may have been affected by menstruation, bleeding haemorrhoids, blood in the urine, medications, vitamins, or foods.

Urinalysis: Blood, glucose, protein, ketones.

Pregnancy: Serum beta-HCG for women of childbearing potential at 4-week intervals.
Urinary beta-HCG for women of child bearing potential at the Follow-up Visit.

Additional laboratory tests will be performed where indicated for patients who report gastrointestinal adverse experiences which are of concern to them or interfere with their daily activities (see [Section 8.1.2](#)).

The central laboratories, SmithKline Beecham Clinical Laboratories (SBCL) and Dorevitch Laboratories (Australia/New Zealand sites only) will be used for the routine haematological and biochemical assessments. All centres will send their samples to the SBCL or Dorevitch Laboratories. Samples must be clearly labelled with the patient number, patient initials, account number and requisition number. Full details for the preparation and shipment of samples will be provided by SBCL/Dorevitch to the Investigator before the start of the study. Urinalysis will initially be performed at the site using a dipstick provided by SBCL/Dorevitch. If abnormalities are found, full microscopy will be performed by SBCL/Dorevitch.

Pregnancy testing at the Follow-up Visit will be performed locally using kits provided by SBCL/Dorevitch.

Reference ranges for all parameters will be obtained from the laboratory prior to starting the study and the tests should not be changed unless absolutely necessary during the study. If a change is unavoidable, the new reference range should be clearly identified in the CRFs concerned.

All clinically significant abnormal laboratory findings are to be repeated until the values return to normal. If such values do not return to normal within a period judged reasonable by the Investigator, the aetiology should be identified and the sponsor notified. Clinically significant worsening in laboratory findings must be recorded in the Adverse Experiences section of the CRF. Values outside of the reference range, but of no clinical significance, should be marked "NCS" by the Investigator on the printed laboratory report sheet.

5.4.4 Diary Card Completion

All visits (except Follow-up)

Diary cards will be issued at all on-therapy visits and will provide space for the patient to record if they feel differently since starting the study medication. This will help the patient to remember experiences that occur between visits that they want to discuss with the Investigator at the next visit.

5.4.5 Pulmonary Function Tests (All Visits Except at Week 1)

Preceding each clinic measurement of respiratory function, patients will have eaten breakfast but withheld the morning dose of study medication prior to the clinic visit, refrained from using inhaled short-acting beta₂-agonists or anticholinergic medications and not smoked for two hours before the visit. In addition, they will have refrained from using long-acting beta₂-agonists for 12-hours before the visit. At all visits, PFTs will be performed in the absence of beta₂-agonists and will be performed at trough (pre-dose) plasma levels of study medication.

Forced expiratory volume in one second (FEV₁), forced expiratory volume in 6 seconds (FEV₆), forced vital capacity (FVC), peak expiratory flow rate (PEFR), forced expiratory flow at 25-75% (FEF₂₅₋₇₅) of vital capacity and forced expiratory flow at 75% (FEF₇₅) of vital capacity will be measured according to the BTPS (Body Temperature and Pressure Standard) convention using the spirometer provided by SB which is suitable for research purposes, calibrated and maintained to acceptable respiratory function laboratory standards. The spirometry equipment provided by SB must be used for this study. All PFTs will

be performed in accordance with the spirometry manual provided to each site. Pulmonary function tests will be performed after the patient has been at rest for at least 10 minutes after an exercise tolerance test. Pulmonary function tests will be repeated up to 8 times to obtain three acceptable readings according to ATS guidelines. [3] For each set of measurements, one FEV₁ must be within 10% of the highest value recorded.

5.4.6 Exercise Tolerance Test (12-week Intervals)

At 12-week intervals and early withdrawal, a 6-minute walk test as described by G. H. Guyatt and colleagues will be used to assess the functional capacity of the patient. [4]

The 6-minute walk will be conducted greater than 2 hours after the patient's last short-acting beta2-agonist or greater than 12 hours after the last long-acting beta2-agonist and where possible should be administered by the same person to avoid interrater variability. The patient will be instructed to walk from one end of a course to the other, covering as much ground as they can during 6 minutes. The patient will be encouraged to perform during the tests; the supervisor will face the patient every 30 seconds and deliver one of the following encouraging phrases:

"You're doing well!" or "Keep up the good work!"

At the end of the test, the supervisor will call out "Stop" and the distance walked by the patient will be measured and recorded on the CRF.

5.4.7 Breathlessness Assessment - Overall (All Visits Except Week 1) and Post-exercise (12-week Intervals, Early Withdrawal)

To assess overall breathlessness, patients will be asked the following question at all visits (except Week 1):

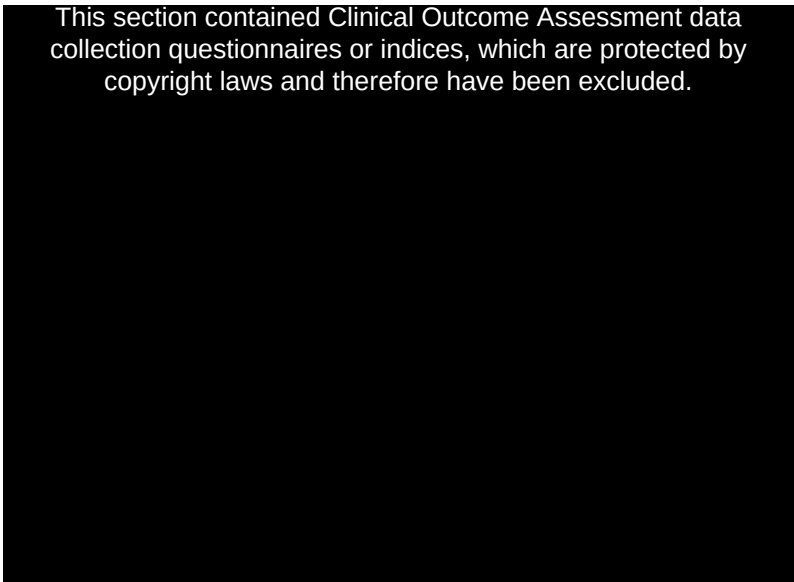
This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

An assessment of breathlessness will also be made immediately following exercise testing at 12-week intervals (e.g., Weeks 12, 24, 36, 48) and at early withdrawal. Patients will be asked the following question:

For each assessment, patients will rate their breathlessness on a scale of 0 to 10, using the modified Borg scale (Table 2). [5] Investigators must show the scale to patients when the assessment is made. Responses are not limited to whole numbers.

Table 1 Breathlessness Assessment

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.



6.0 Study Medication

6.1 Study Medication

SB 207499 will be provided as a film-coated, octagonal, yellow "Tiltab" tablet containing 15 mg of SB 207499.

6.2 Dosage and Administration

Patients will take one tablet in the morning after breakfast (ideally at 08:00) and one tablet after their evening meal (ideally at 20:00).

Tablets should be ingested with a glass of water. At each visit, patients will be instructed by the Investigator to attend the next visit not having taken the morning dose of study medication. These doses will be taken during the clinic visits (with food) at the instruction of the Investigator. **Note: The first dose of study medication for patients transferring from study 042 will not be taken at the first clinic visit of study 040. Instead, patients will take the first dose of study 040 medication in the evening allowing at least 8 hours since the last dose of study 042 medication taken in the clinic that morning.**

6.3 Method of Blinding

This is an open study.

6.4 Packaging

SB 207499 tablets will be provided in bottles containing either 70 or 210 tablets, corresponding to a 35-day or 105-day supply of study medication. Study medication will be issued at each clinic visit. For visits at 4-weekly intervals, one bottle of 70 tablets will be issued at each visit. For visits at 12-weekly intervals, either three bottles of 70 tablets, or one bottle of 210 tablets will be issued.

6.5 Labelling and Preparation

Patients will retain their patient identification number (PID) from study 042 or study 091. Study medication labels for all patients will not have pre-printed PIDs. Investigators must transcribe the patient initials, date dispensed and visit number for the patient onto the study medication labels.

A two-panel label consisting of a fixed portion and a tear-off portion will be attached to the medication bottles. The Investigator or his/her designate will remove the tear-off label from the bottle at the time of dispensing and attach it to the appropriate page in the CRF.

Labels will contain the following:

- Space to enter patient initials
- Space to enter date dispensed
- Space to enter visit number
- Description of contents
- Protocol number
- Dosing directions
- Storage conditions (room temperature)
- Packaging (job) number
- Batch number of tablets
- Keep out of reach of children
- Appropriate caution statements
- Company address
- Any other information specified by local regulatory requirements

6.6 Storage

Prior to dispensing, all study medication will be kept safely locked in a dry place at room temperature (at or below 30°C).

6.7 Drug Accountability

At the time of delivery of medication to the study site, the Investigator or designate will sign a Drug Receipt Form to confirm that the supplies for the study have been received. This form will specify supply or lot numbers, quantities shipped/delivered, and the date of receipt. The form will also contain statements confirming that

- The investigational products will be handled and stored safely and properly
- The investigational products will be dispensed only to patients in accordance with the protocol
- Any unused products will be returned to SmithKline Beecham.

The Investigator or designate will record all study medication dispensed on a Drug Accountability Form. At the conclusion of the study, reconciliation must be made between the amount of medication supplied, dispensed, and subsequently returned to SB. Any discrepancies must be accounted for. A certificate of return must be signed incorporating the assurance from the Investigator or designate that all used and unused investigational products have been returned. In the majority of cases, supplies will be returned to SB for subsequent destruction. In exceptional cases, supplies may be destroyed at the centre. Destruction should only be performed by authorised personnel who are aware of any possible hazardous effects, and following receipt of written approval from SB. The procedure should be documented in full, in writing.

6.8 Assessment of Compliance

Counts of tablets returned will be made at the beginning of all visits. Compliance (%) will be calculated according to the equation below and entered into the CRF:

$$\frac{\text{Number of tablets dispensed} - \text{number of tablets returned or lost}}{2 \times \text{number of days since last visit}} \times 100$$

Patients who show <80% or >120% compliance in taking study medication at two consecutive visits will not be permitted to continue in the study. Investigators will emphasise the importance of compliance in taking study medication to patients who are non-compliant after 1 week in the study (Visit 2).

6.9 Treatment of Study Medication Overdosage

Treatment of any suspected or confirmed overdose with SB 207499 should be symptomatic. Any instance of a suspected or confirmed overdose must be fully documented as a serious adverse experience and communicated to the SB Medical Monitor within 24 hours ([Section 8.6](#)).

6.10 Occupational Safety

Study medications are not expected to pose significant occupational safety risks to investigational staff under normal conditions of use and administration. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions is available upon request.

6.11 Concomitant Medication/Treatment

All concomitant medications taken during the study must be recorded in the CRF with the indication, unit dose and frequency, and dates of administration.

6.11.1 Inhaled Bronchodilators

The use of on-demand inhaled beta₂-agonists will be permitted throughout the study on an "as needed" basis, and will be recorded on the concomitant medication section of the CRF. Patients may continue to use whichever beta₂-agonists they use regularly. Investigators must note the name of the beta₂-agonists and strength per actuation in the CRF.

6.11.2 Anticholinergic Agents

The use of anticholinergic medication will be permitted during the study. Patients should continue to use their regular inhaler devices. Where possible, the dose of the medication should remain stable throughout open-label treatment. The use of inhaled anticholinergic medication must be recorded in the concomitant medication section of the CRF.

6.11.3 Other Concomitant Medications

There are no restrictions on the use of any concomitant COPD medication during the study with the exception of theophylline and aminophylline (oral or intravenous). Where possible, other COPD medication should be administered at stable doses. All concomitant medication taken during the study will be recorded in the CRF together with indication, daily dose, and dates of administration.

7.0 Outcomes Research and Pharmacoeconomics

7.1 Medical Care Utilisation Data Collection and Analysis

Medical care utilisation data will be collected in association with COPD disease exacerbations which require healthcare professional or medical intervention. Medical care utilisation includes hospitalisation, length of stay in intensive care units, emergency room visits, non-protocol physician office visits, physician office phone contacts for advice on management of an exacerbation, and medications used in the treatment of a COPD exacerbation (antibiotics, oral corticosteroids, beta₂-agonist via nebuliser or injection and oxygen). The medical care utilisation information will be collected in the CRF. Non-protocol medications used for the treatment of an exacerbation of COPD will be collected in the CRF.

7.2 Costs Associated With Lost Work Productivity

Data will be collected at each visit on the number of workdays lost as a result of an exacerbation episode. These data should be recorded in the CRF.

7.3 Quality of Life Analyses

Short-Form 36 (Appendix D)

The MOS Short-Form 36 is a generic quality of life assessment tool which has been used extensively to evaluate the physical, mental and general health status of patients. [6] The SF-36 will be administered at Week 0 and at 24-week intervals. Any patient who withdraws from the study should complete the SF-36 at the time of withdrawal (Section 5.3.8). The SF-36 will be scored using the standard scoring methodology described in the SF-36 reference manual. [7]

St. George's Respiratory Questionnaire (Appendix E)

It is clear that there is no universally accepted score for assessing symptoms in patients with COPD. The St. George's Respiratory Questionnaire (SGRQ) is a symptom-based, disease-specific quality of life instrument. [8,9,10] Advantages of using the SGRQ above other symptom-based assessments of disease status include the fact that it is validated in a number of different European languages

and American English and a minimum clinically meaningful difference has been defined (4 unit change compared to placebo). [10]

The SGRQ is a self-administered questionnaire designed to measure and quantify the impact of chronic respiratory disease on health related quality of life and well-being. The SGRQ measures the impact of chronic respiratory disease on three domains: symptoms, activity and impact (on daily life). A total score is calculated for the entire questionnaire and for the 3 component domains. Guidelines for completion of the SGRQ are provided in [Appendix E](#).

The SGRQ will be administered at Week 0, Week 12, Week 24 and at 24-week intervals thereafter. Any patient who withdraws from the study should complete the SGRQ at the time of the withdrawal ([Section 5.3.8](#)).

8.0 Adverse Experiences

The recording of adverse experiences is an important aspect of study documentation. Detailed guidelines are described in this section.

8.1 Eliciting and Documenting Adverse Experiences

It is the responsibility of the Investigator to document all adverse experiences which occur during the investigation.

An adverse experience includes any noxious, pathological or unintended change in anatomical, physiological or metabolic functions as indicated by physical signs, symptoms and/or laboratory changes occurring in any phase of the clinical study, whether associated with the study drug or placebo, and whether or not considered drug related. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction or the significant worsening of the disease under investigation that is not recorded elsewhere in the CRF under specific efficacy assessments. Anticipated day-to-day fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening need not be considered adverse experiences. Discrete episodes of chronic conditions occurring during a study period should be reported as adverse experiences in order to assess changes in frequency or severity.

An adverse experience should be documented in terms of a medical diagnosis. When this is not possible, the adverse experience should be documented in terms of signs and/or symptoms observed by the Investigator or reported by the patient at each study visit.

Any pre-existing conditions or signs and/or symptoms present in a patient should have been recorded on the Medical/Surgical History form or as Adverse Experiences within the patient's CRF for study 042 and study 091.

All adverse experiences occurring after administration of the first dose of study medication (i.e., active drug) and on or before the final visit, must be reported on the Adverse Experience page in the patient's CRF, REGARDLESS OF WHETHER OR NOT THEY ARE CONSIDERED DRUG RELATED.

Serious adverse experiences which occur during the clinical study or within 30 days of receiving the last dose of study medication, whether or not related to study drug, must be reported.

Instances of death, cancer or congenital abnormality, if brought to the attention of the Investigator AT ANY TIME after cessation of study medication AND considered by the Investigator to be possibly related to study medication, should be reported to the SB Medical Monitor.

At each visit/assessment, adverse experiences will be evaluated by the Investigator. Adverse experiences not previously documented in the study will be recorded in the Adverse Experience Section of the patient's CRF. The nature of each experience, date and time (where appropriate) of onset, outcome, course (i.e., intermittent or constant), maximum intensity, action taken with respect to the investigational drug and relationship to treatment should be established. Details of changes to the dosage schedule or any corrective treatment should be recorded on the appropriate pages of the CRF.

Adverse experiences already documented in the CRF (i.e., at a previous assessment and designated as ongoing) should be reviewed at subsequent visits as necessary. If these have resolved, the documentation in the CRF should be completed. If an adverse experience changes in frequency or severity during a study period, a new record of the experience will be started.

As a consistent method of soliciting adverse experiences, ask the patient a non-leading question such as:

"Have you felt different in any way since starting the new treatment or since the last visit?"

In order to help the patient to remember and to answer this question accurately, the diary will provide space in which the patient may record if they felt different since starting the study medication.

8.1.1 COPD Exacerbation Definitions

An exacerbation of COPD is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.

Investigators will decide whether an exacerbation has occurred and the details will be recorded in a specific COPD exacerbation section of the CRF. COPD exacerbations are categorised as Level 1, 2, or 3, based on the treatment received by the patient for the exacerbation. The levels of exacerbations will be rated as follows:

Level 1 Exacerbation: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2 Exacerbation: Acute worsening of COPD that requires additional treatment (e.g., a short course of oral steroids, antibiotics, etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3 Exacerbation: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

If a patient has an exacerbation of COPD that is longer than 2 weeks in duration during the study, the Investigator will contact the SB Medical Monitor regarding the patient's continuation in the study.

Note: All exacerbations of COPD must be recorded in the COPD exacerbation section of the CRF. Any exacerbation of COPD, regardless of level, that fulfils the SAE criteria must be recorded in the COPD SAE pages of the CRF.

8.1.2 Gastrointestinal Adverse Experiences

Adverse experiences related to the gastrointestinal tract will be closely monitored during this study. Patients will be instructed to call the Investigator to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The Investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of occurrence. This assessment will include a structured history of the adverse experience including relationship to the time of dosing with study medication and food intake; a physical examination with emphasis on the abdomen; and an assessment of orthostatic changes in heart rate

and blood pressure. In addition, laboratory assessments will be performed: complete blood count with white cell differential; amylase, electrolytes, blood glucose, and liver function tests; urinalysis including microscopic examination, if indicated; and a faecal occult blood test. If a faecal occult blood test is positive, the patient will be referred to a gastroenterologist for a colonoscopy that includes visualisation of the transverse colon with reporting of positive or negative findings, irrespective of other identified pathology or causes for gastrointestinal bleeding. Biopsies should be taken if appropriate. Results of the colonoscopy should be faxed to the Sponsor as soon as available. If indicated, additional testing will be performed at the discretion of the Investigator and reports faxed to the Sponsor as soon as available..

Within 24 hours of notification by the patient, the Investigator will complete the GI AE Supplemental Form and fax it to the SB Medical Monitor.

The Investigator will review the results of the initial assessment and arrange further follow-up as appropriate. All events should be followed to resolution. If the patient experiences symptoms which are severe or persistent and considered by the Investigator to be study-drug related, withdrawal of the patient should be considered. Detailed guidelines for the assessment of gastrointestinal adverse experiences are presented in [Appendix F](#).

8.2 Assessment of Intensity

Maximum intensity of adverse experiences should be assigned to one of the following categories:

- Mild: An adverse experience which is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An adverse experience which is sufficiently discomforting to interfere with normal everyday activities.
- Severe: An adverse experience which prevents normal everyday activities.

8.3 Assessment of Causality

Every effort should be made by the Investigator to explain each adverse experience and assess its relationship, if any, to study drug treatment. Causality should be assessed using the following categories: not related, unlikely, suspected (*reasonable possibility*), and probable.

- Not related: The adverse experience is definitely not related to the study medication.
- Unlikely: There are other, more likely causes and the drug is not suspected as a cause.
- Suspected (*reasonable possibility*): A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but *there is a reasonable possibility that the experience was caused by the study medication*.
- Probable: There probably is a direct cause and effect relationship between the adverse experience and the study drug.

The degree of certainty with which an adverse experience is attributed to drug treatment or alternative causes (e.g., natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the experience can be understood in terms of one or more of the following:

- Known pharmacology of the drug
- Reaction of similar nature being previously observed with this drug or class of drug
- The experience having often been reported in literature for similar drugs as drug related (e.g., skin rashes, blood dyscrasia)
- The experience being related by time to drug ingestion terminating with drug withdrawal (dechallenge) or reproduced on rechallenge

8.4 Following-up of Adverse Experiences

Investigators should follow up patients with adverse experiences until the event has subsided (disappeared) or until the condition has stabilised. Reports relative to the patient's subsequent course of an adverse experience noted for any patient must be submitted to the SB Medical Monitor.

8.5 Serious Adverse Experiences

8.5.1 Definition of Serious Adverse Experiences:

A serious adverse experience is any event which is fatal, life threatening, disabling or incapacitating, or results in hospitalisation, prolongs a hospital stay or is associated with congenital abnormality, cancer or overdose (either accidental or

intentional). In addition, any experience which the Investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug will be documented as a serious event.

Definition of "life threatening":

An adverse experience is life threatening if the patient was at immediate risk of death from the event as it occurred (i.e., it does not include a reaction that, if it had occurred in a more serious form, might have caused death). For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug induced hepatitis can be fatal.

Definition of "disabling/incapacitating":

An adverse experience is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the patient's ability to carry out normal life functions.

Definition of "hospitalisation":

Adverse experiences that require hospitalisation should be considered serious. Hospitalisation for elective surgery or routine clinical procedures that are not the result of an adverse experience (e.g., elective surgery for a pre-existing condition) need not be considered adverse experiences and should be recorded on the Medical/Surgical Procedures form in the CRF. If anything untoward is reported during the procedure, that occurrence must be reported as an adverse experience, either "serious" or "non-serious" according to the usual criteria.

In general, hospitalisation signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. When in doubt as to whether "hospitalisation" occurred or was necessary, the adverse experience should be considered serious.

Definition of "routine clinical procedure":

One which is defined in the protocol as a procedure which may take place during the study period and should not interfere with the study drug administration or any of the ongoing protocol specific procedures.

8.5.2 Reporting Serious Adverse Experiences

Any serious adverse experiences which occur at any time during the clinical study or within 30 days (or five half-lives, whichever is longer) of receiving the last dose of study medication, whether or not related to the study drug, must be reported by the Investigator to the local SB Medical Monitor by fax or telephone within 24 hours. If the GI AE of Concern also meets the criteria for a serious adverse event (SAE), the GI AE Supplemental Form, the Serious Adverse Experience CRF pages, CRF demography, medical history, prior/concomitant medications, study medication records, will also be faxed to GSK within 24 hours of notification by the patient.

Investigators should not wait to receive additional information to fully document the event before notifying SB of a serious adverse experience. The fax or telephone report should be followed by a full written summary utilising the SB Serious Adverse Experience form detailing relevant aspects of the adverse experience(s) in question. Where applicable, information from relevant hospital case records and autopsy reports should be obtained.

Instances of death, cancer or congenital abnormality, if brought to the attention of the Investigator AT ANY TIME after the cessation of study medication AND considered by the Investigator to be possibly related to study medication, should be reported to the SB Medical Monitor.

8.6 Reporting of Overdose

Any instance of overdose (suspected or confirmed, whether or not it involves the study medication) must be communicated to SB within 24 hours and be fully documented as a serious adverse experience. Details of any signs or symptoms and their management should be recorded including details of any antidote(s) administered ([Section 6.10](#)).

8.7 Pregnancy

Patients who become pregnant during the study should be withdrawn from the study immediately.

Patients should be instructed to notify the Investigator if it is determined after completion of the study that they became pregnant either during the treatment phase of the study or within 30 days after the treatment period.

Whenever possible, a pregnancy should be followed to term, any premature terminations reported and the status of the mother and child after delivery should be reported to SB.

9.0 Patient Completion and Withdrawal

9.1 Definitions

Premature termination is defined as withdrawal of the patient for any reason before registration of the compound or project termination.

9.2 Procedures for Handling Withdrawals

Patients who terminate their participation in the study because of adverse experiences should be followed up as appropriate ([Section 8.4](#)) in order to determine the final outcome of the adverse experience.

All patients who withdraw or are withdrawn from the study should complete the assessments and procedures scheduled for early withdrawal ([Section 5.3.8](#)), wherever possible.

The CRFs of *all* patients entered into the study must be kept, and the reasons for withdrawal will be noted on the study conclusion page for all enrolled patients who do not complete the study. In addition, the date of the last dose of study medication must be recorded on the study conclusion page for all patients withdrawn from the study.

9.3 Reasons for Withdrawal

Every effort must be made by the Investigator to keep patients in the study. However, a patient may be discontinued prior to completion of the study for the following reasons:

- **Adverse experience** ([Section 8.0](#)): This includes a deterioration in COPD or COPD exacerbation resulting in a patient being withdrawn.
- **Lack of efficacy**: This includes a desire by the patient/Investigator that the patient be withdrawn from the study because of no improvement in COPD symptoms. It **does not** include a deterioration in COPD or COPD exacerbation which must be regarded as an adverse experience.

- **Conduct of Study Deviation:** This includes lack of compliance (dosing, visit schedule).
- **Patient lost to follow-up**
- **Termination** of the study by SmithKline Beecham
- **Other** (reason to be documented in the CRF).

All adverse experiences leading to withdrawal of a patient must be fully documented and followed-up as appropriate ([Section 8.0](#)). To ensure that all withdrawals due to adverse experiences are correctly identified, "Adverse Experience" should only be checked as the reason for withdrawal on the Study Conclusion page for those patients for whom an adverse experience was considered to be the direct cause of the patient withdrawing from the study. This is particularly important when adverse experiences are ongoing at the time of withdrawal but the reason for withdrawal is not related to the adverse experiences.

10.0 Data Evaluation

The Biometrics Unit of SmithKline Beecham Pharmaceuticals will perform all statistical analyses.

10.1 Target Sample Size

No formal power calculations were performed since this is an open-label study with the primary purpose of evaluating patient safety. It is estimated that approximately 600 patients will be enrolled at 200 centres in Europe, South Africa and Australia/New Zealand participating in study 042 or study 091.

10.2 Method of Randomisation

This is an open-label study. All patients will receive SB 207499 15 mg bid.

10.3 Planned Efficacy Analysis

10.3.1 Efficacy Variables

- Clinic trough FEV_1 , FEV_6 , FVC, FEF_{25-75} , FEF_{75} , and PEFr
- Overall and post-exercise breathlessness (Borg scale)

- Total and subscale scores of the SGRQ
- Exercise performance (distance walked during 6-minute walk)
- SF-36 (generic quality of life)
- COPD exacerbation rates
- Health economic measures (days off work, healthcare utilisation)

10.3.2 Derivation of Efficacy Variables for Analysis

For each clinic pulmonary function parameter, three adequate readings will be collected at each scheduled evaluation. The highest of the three readings will be used in the analysis. If more than one set of readings is available for a particular assessment, the later of the two readings will be used in the analysis. For the SGRQ and SF-36 scores will be derived according to algorithms provided by the scales developers. Change from baseline will be calculated for all continuous efficacy parameters as the difference between the visit evaluation and the baseline evaluation. Baseline is defined as the predose evaluation at Visit 3 of the parent study.

10.3.3 Populations to be Evaluated

All efficacy analyses will be based on the population of patients who receive at least one dose of study medication and have at least one efficacy evaluation during the study. Description of efficacy variables will be by randomised treatment group in the parent study.

If there is adequate sample size additional analyses will be performed based on use of concomitant COPD medication use.

10.3.4 Comparisons of Interest

The primary comparison of interest will be the within group change from the baseline assessment of the parent study (study 042 and study 091).

An additional comparison will be a within group change from Visit 1 of study 040 for patients randomised to placebo in the parent study.

No comparison between the two groups will be performed.

10.3.5 Methods of Analysis

Descriptive statistics will be provided for all demographic and baseline characteristics.

For continuous efficacy endpoints defined in [Section 10.3.1](#), descriptive statistics (including mean, median, range, standard deviation and 95% confidence intervals) will be provided for the change from baseline at each scheduled study visit. No statistical hypothesis testing will be performed.

Annualised rates for COPD exacerbations and resource utilisation will be estimated using a Poisson regression model.

10.4 Planned Safety Evaluation

Evaluation of safety data will include all patients who receive at least one dose of study medication. Primary consideration will be given to presentation of the safety data without regard to randomised treatment in the feeder study. A secondary presentation of safety data will be by randomised treatment in the feeder study.

Adverse experiences will be summarised by time to onset, severity, and Investigator-reported relationship of the adverse experience to study medication. Gastrointestinal adverse experiences of concern will be summarised separately. The proportion of patients withdrawn due to adverse experiences and due to gastrointestinal adverse experiences of concern will be evaluated.

For clinical laboratories, vital signs and ECG intervals descriptive statistics will be provided at each visit. For clinical laboratories the percentage of patients outside the normal limits and with values of sponsor-defined clinical concern will be tabulated across all on-therapy visits. Vital signs of clinical concern, orthostatic vital signs of clinical concern and ECGs of clinical concern will be tabulated in similar manner. Orthostatic vital signs of clinical concern will be summarised for all patients enrolled and the subgroup of patients with gastrointestinal adverse experiences of concern. Clinical concern criteria will be documented separately. In addition ECG abnormalities will be summarised using SNOMED terminology.

The proportion of patients with positive faecal occult bloods on-therapy will be tabulated for all enrolled patients and the subgroup of patients with gastrointestinal adverse experiences of concern.

Exploratory analyses will be performed to further characterise gastrointestinal adverse experiences of concern.

10.5 Interim Analysis

This is an open-label study. Data will be evaluated on an ongoing basis.

11.0 Administrative Matters

To comply with Good Clinical Practice, important administrative obligations relating to Investigator responsibilities, monitoring, archiving data, audits, confidentiality and publications must be fulfilled as given in [Appendix B](#).

12.0 References

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13.0 Appendices

Appendix A: World Medical Association Declaration of Helsinki

Recommendations guiding physicians in
biomedical research involving human subjects

Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964

Amended by the 29th World Medical Assembly,
Tokyo, Japan, October 1975

35th World Medical Assembly,
Venice, Italy, October 1983

and the

41st World Medical Assembly
Hong Kong, September 1989

and the

48th General Assembly

Somerset West, Republic of South Africa, October 1996.

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration", and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice, most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognised between medical research in which the aim is essentially diagnostic or therapeutic

for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings for further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

- 1 Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
- 2 The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the Investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
- 3 Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
- 4 Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
- 5 Every biomedical research project involving human subjects should be preceded with careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

- 6 The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
- 7 Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
- 8 In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
- 9 In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.
- 10 When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case, the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.
- 11 In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
- 12 The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical Research)

- 1 In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.
- 2 The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
- 3 In any medical study, every patient including those of a control group, if any, should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
- 4 The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
- 5 If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I,2).
- 6 The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-Clinical Biomedical Research)

- 1 In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
- 2 The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.
- 3 The Investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.
- 4 In research on man, the interest of science and society should never take precedence over considerations related to the well being of the subject.

Appendix B: Administrative Matters

I. RESPONSIBILITIES OF THE INVESTIGATOR

- To ensure that he/she has sufficient time to conduct and complete the study, and has adequate staff and appropriate facilities which are available for the duration of the study, and to ensure that other studies do not divert essential subjects/patients or facilities away from the study at hand.
- To submit an up-to-date curriculum vitae and other credentials to the sponsor and - where required - to relevant authorities.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the Laboratory License or Certification.
- To prepare and maintain adequate case histories designed to record observations and other data pertinent to the study.

II. PROTOCOL AMENDMENTS

No changes to the study protocol will be allowed unless discussed in detail with the SmithKline Beecham (SB) Medical Monitor and filed as an amendment/modification to this protocol.

Any amendment/modification to the protocol will be adhered to by the participating centre (or all participating centres) and will apply to all subjects following approval as appropriate by the Ethical Review Committee or Institutional Review Board.

III. SPONSOR'S TERMINATION OF STUDY

SB reserves the right to discontinue the clinical study at any time for medical or administrative reasons. When feasible, a 30-day written notification will be tendered.

IV. CASE REPORT FORM INSTRUCTIONS

Prior to screening the first potential participant, the Investigator will provide a list showing the signature and hand-written initials of all individuals authorised to

make or change entries on CRFs. If the authorised individuals should change during the study, the Investigator is to inform SB.

CRFs will be supplied by SB for recording all data. It is the responsibility of the Investigator to ensure that CRFs are legible and completely filled in with a black ink ball-point pen. The subject's identification (2-3 alphabetic letters representing the subject's initials or first letter of subject's name), the patient identification (PID) if not already pre-printed and the visit date will be entered on the CRF Header Pages as required.

Errors must be corrected by drawing a single line through the incorrect entry and writing in the new value/data positioned as close to the original as possible. The correction must then be initialled, dated and justified by the authorised individual making the change. Do not obliterate, write over or erase the original entry when making a correction.

When a subject completes a visit, it is anticipated that relevant sections of the CRF will be completed by the Investigator (or designated staff member) within 24 hours of the last data becoming available, but in no case later than five days. Similarly, when a subject completes a study, it is anticipated that all relevant CRF pages will be completed within 24 hours of the last data becoming available, but in no case later than five days. This also applies to forms for potential study participants who were not randomised to a treatment group.

As soon as the subject has completed/withdrawn from the study and the CRF is completed, the principal Investigator or designated physician(s) under his/her supervision will sign the adverse experience page(s) as well as study conclusion page of the CRF to confirm that they have reviewed the data and that the data are complete and accurate. If sections of a CRF are to be brought into SB prior to study conclusion, a Section conclusion signature is required.

An original (top copy) CRF must be submitted for all subjects who have undergone protocol specific procedures, whether or not the subject completed the study.

While completed CRFs will be reviewed by an SB professional monitor at the study sites, errors detected by subsequent in-house CRF review may necessitate clarification or correction of errors and documentation and approval by the Investigator.

Any questions or comments related to the CRF should be directed to the assigned SB Medical Monitor.

V. MONITORING BY SMITHKLINE BEECHAM

Monitoring visits by a professional representative of SB (the sponsor) will be scheduled to take place before study initiation and at appropriate intervals during the trial and after the last subject has completed the study.

These visits are for the purpose of verifying adherence to the protocol and the completeness and exactness of data entered on the CRF and Drug Inventory Forms. The monitor will verify CRF entries by comparing them with the hospital/clinic/office records which will be made available for this purpose. The monitor will retrieve completed CRF sections at each visit. Adequate time and space for these visits must be made available by the Investigator.

The Investigator must ensure provision of reasonable space and adequate qualified personnel for monitoring visits.

VI. ARCHIVING OF DATA

The Investigator must retain subject records, CRFs and drug disposition records in an easily retrievable form for 15 years after completion or until disposal has been agreed in writing with SB, whichever is sooner. The Investigator must have a 'key' linking the subject's study identification number (i.e., treatment number) to the subject's clinical file. If the Investigator moves or retires, he/she must nominate someone in writing to be responsible for record keeping. Archived data may be held on microfiche or electronic record, provided that a back-up exists and a hard copy can be obtained from it, if required.

SB agrees to retain a copy of the protocol, documentation, approvals and all other documents related to the study, including certificates that satisfactory audit and inspection procedures have been carried out. SB also agrees to provide copies to the Investigator should he/she wish another copy.

VII. AUDITS

For the purpose of compliance with Good Clinical Practice and Regulatory Agency Guidelines, it may be necessary for SB or a Drug Regulatory Agency to conduct a site audit. This may occur at any time from start to after conclusion of the study.

When an Investigator signs the protocol, he agrees to allow the Drug Regulatory Agency and SB auditors to inspect his/her study records. Furthermore, if an Investigator refuses an inspection, his data will not be accepted in support of a New Drug Registration and/or Application.

SB has a substantial investment in clinical studies. Having the highest quality data and studies are essential aspects of drug development. SB has a Regulatory Compliance staff who audits investigational sites. Regulatory Compliance assesses the quality of data with regard to accuracy, adequacy and consistency. In addition, Regulatory Compliance assures that SB-sponsored studies are conducted in accordance with Good Clinical Practices standards and that relevant regulations/guidelines are being followed.

To accomplish these functions, Regulatory Compliance selects investigational sites to audit. These audits usually take one to two days. The SB audits entail review of source documents supporting the adequacy and accuracy of CRFs, review of documentation required to be maintained and checks on drug accountability. The SB audit therefore helps prepare an Investigator for a possible regulatory agency inspection, as well as assuring SB of the validity of the database across investigational sites.

The Inspector will be especially interested in the following items:

- Log of visits from the sponsor's representatives
- IRB/ERC approval
- Study medication accountability
- Approved study protocol and amendments
- Signed informed consent of the subjects
- Medical records including laboratory data to support entries in the CRF
- Correspondence between the IRB/ERC and the sponsor
- Record retention

SB will gladly assist investigators prepare for a regulatory agency inspection.

VIII. CONFIDENTIALITY AND PUBLICATION

The Investigator agrees that all information provided by SB is the exclusive property of SB and that the same shall be kept strictly confidential by the Investigator or any other person connected with the work and shall not be disclosed by the Investigator or such person to any third party without the prior written consent of SB. The Investigator shall communicate the results of the work promptly to SB.

SB agrees that the Investigator shall have the right to publish or permit the publication of any information or material relating to or arising out of the work after prior submission to SB provided that, if SB shall so requests, the Investigator will delay publication for a maximum of six months to enable SB to protect its rights in such information or material. Any proposed publication or presentation (e.g., manuscript, abstract or poster) for submission to a journal or scientific meeting should be sent to the SB Medical Monitor prior to submission. SB will undertake to comment on such documents within four weeks.

All rights and interests world-wide in any inventions, know-how or other intellectual or industrial property rights which arise during the course of and/or as a result of the clinical study which is the subject of this Protocol or which otherwise arise from the information or materials supplied under this Agreement, shall be assigned to, vest in and remain the property of SmithKline Beecham plc.

Appendix C: Sample Informed Consent

WRITTEN INFORMED CONSENT TO PARTICIPATE IN A CLINICAL STUDY OF AN INVESTIGATIONAL DRUG

INVESTIGATOR: (Name, Address, Phone)

STUDY TITLE: A multicentre, open-label extension study to evaluate the safety, tolerability and efficacy of oral SB 207499 (15 mg twice daily) in patients with chronic obstructive pulmonary disease (COPD).

PROTOCOL NO.: 207499/040

SPONSOR: SmithKline Beecham Pharmaceuticals ("The Company")

Dear Patient

We would like you to consider taking part in this medical research study assessing the long-term safety and effectiveness of a new treatment - "SB 207499" because you suffer from chronic obstructive pulmonary disease (COPD). This is an extension study to the previous study (study 042 or study 091) which you have completed.

However, before you decide whether or not to take part, please read the following information carefully and ask any questions you have. Before taking part in the study, it is necessary for you to give your written consent to participate.

Nature and Purpose of the Study

SB 207499 is a new type of drug called a "phosphodiesterase inhibitor".

Phosphodiesterases, which are substances in the body, may be involved in producing some of the symptoms of COPD. If the effects of phosphodiesterases in the lungs can be blocked by SB 207499, the course of COPD may be improved.

To date, SB 207499 has been given to 1068 patients with COPD and asthma in research studies. These studies have shown that the new medication appears to be safe and data from a study in patients with COPD showed that the dose to be used in this study was of benefit by reducing symptoms and improving lung function. The most common side effects known at this time are headache, nausea,

diarrhoea, abdominal pain, indigestion and vomiting, the majority of which have been mild or moderate and have not required treatment. Due to these side effects being mostly gastrointestinal (in the stomach area) you will be asked to make a note of these symptoms in a diary card during the study to better describe the nature of these symptoms. In addition, if you experience gastrointestinal symptoms that are of concern to you or interfere with your daily activities you should contact your study doctor as soon as possible so she/he can decide whether other tests are appropriate.

In this study you are given two tablets of medication per day (each containing 15 mg of SB 207499). One tablet should be taken immediately after your breakfast and the other tablet taken immediately after your evening meal each day.

What Does the Study Involve

This extension study is planned to last until SB 207499 is registered or the project is terminated by the company. It is anticipated that approximately 600 patients will take part in this study. Before starting the study, you will have given your written consent to take part.

If you qualify for the study, you will be given the study medication. You will also be asked to complete a diary card to write down if you feel differently since starting study medication and to record the date of onset.

You will be asked to visit the clinic weekly for two weeks, then once a fortnight and then every month. Once you have completed at least one year in the study, you will be asked to visit the clinic every three months. You should make sure that you have eaten breakfast and that you do not take your morning dose of study medication before each visit. Also, you will be asked not to use your inhaler(s) or smoke for 2 hours before the visits or during the clinic visit.

The following tests will be carried out:

- Lung function tests (spirometry) will be measured at every visit (except the 2nd Visit).
- A physical examination will be performed at visits 1, 9 and 15 and then every 24 weeks.
- Blood pressure and heart rate will be measured at every visit.
- At each visit you will have small wires stuck to your body at several places to record an (ECG). This will measure the electrical activity of your heart.

- An exercise test, involving 6 minutes of walking, will be carried out at visits 1, 6, 9, 12 and 15 and then every 12 weeks to look at how well your lungs work during exercise. After walking, your heart rate and the amount of oxygen in your bloodstream will be measured through your skin with a device clipped on your finger or ear.
- Blood (20mls) and urine(10mls) samples for routine laboratory tests will be taken at every visit. Pre-menopausal women will be asked to produce one urine sample for pregnancy testing at the Follow-up visit.
- You will be given questionnaires to complete at visits 1, 6, 9 and 15 and then every 24 weeks to assess your quality of life.
- Three pea-sized faecal samples will be requested for collection at 24 weeks, 48 weeks and annually thereafter and if you withdraw early from the study to test for bleeding in your gastrointestinal system. Three tests collected on consecutive bowel movements, if possible, are to be performed according to the instructions provided with the faecal occult blood kits. In particular, you will be asked not to collect samples during or until 3 days after a menstrual period or while you have bleeding haemorrhoids or blood in the urine. You will be asked to avoid taking aspirin or other non-steroidal anti-inflammatory drugs (such as ibuprofen or naproxen) for 7 days before and during the test period. For 72 hours before and during the test period, you will be asked NOT to take more than 250 mg of Vitamin C per day and NOT to eat red meat (including processed meats and liver) or raw fruits and vegetables (especially melons, radishes, turnips, and horseradish). When the samples are returned for analysis, the Investigator will ask if you followed the instructions.
- After the last visit, you will be asked to return to the clinic for a safety follow-up visit where a physical examination, ECG and blood sample may be requested by your doctor.

Certain medications are not allowed during the study. Your doctor will give you a list of these prohibited medications. Also please check with your doctor before taking any 'over-the-counter' medications.

Pregnancy

The effects of SB 207499 on an unborn baby are uncertain and so you will not be allowed to participate in this study if you are pregnant. If there is any chance you could become pregnant during the study, you must use one of the allowed contraceptive methods. Also, if appropriate, you will be tested during the study to determine whether you might have become pregnant. If you do become pregnant you must stop taking the study medication immediately and contact your doctor.

You should also tell your doctor if you become pregnant within a month of completing the study.

What are the Risks Associated with the Study

All drugs may cause side-effects in some patients. At the dose used in this study, the most common side-effect of SB 207499 known at this time are headache, nausea, diarrhoea, abdominal pain and indigestion. Vomiting and dizziness have also been observed in some volunteers, but generally at higher doses than that being studied here and these side-effects resolved with no treatment. In the interest of your safety, SB is researching these gastrointestinal complaints. If you experience black or bloody stools, abdominal discomfort, such as pain or cramps, diarrhea, or vomiting that cause you concern or interfere with daily activities (including eating or sleeping), you will be asked to contact your Investigator and you will visit the clinic within 24 hours. At the clinic, your doctor will discuss the complaint with you, complete a physical examination of the abdomen, and measure your blood pressure in the lying and sitting positions. Blood will be drawn and you will give a sample of urine. Your doctor will also give you a faecal occult blood test kit to test for gastrointestinal bleeding. You will use this kit to obtain small stool samples at home to be returned to the clinic for analysis. The doctor will ask if you have been menstruating, had bleeding haemorrhoids, or had blood in the urine, and will also question you about the medications, vitamins, and foods you have been taking. If the faecal occult blood test indicates that you have blood in your stool, you will be referred to a gastroenterologist for a colonoscopy. You will also be referred for a colonoscopy if you have black, tarry, or bloody stools or if you pass blood from the rectum. Additional tests or procedures might be performed at the discretion of your doctor. Your progress will be followed daily thereafter until you feel better and you and your doctor decide that the problem is resolved.

Certain procedures, including some lung function tests, heart rate and blood pressure monitoring, form part of the study. These investigations would normally be carried out by a doctor in routine examination of your condition. However, during this study ECG recordings will also be made and blood samples will be taken. You may experience some discomfort and bruising at the injection site where you have blood taken from. The drugs used in this study may involve other risks that are not known at this time.

What are the Benefits

You and other patients with COPD in the future may benefit from any experimental research. Such benefits include the possibility that your condition may improve and that this study may help develop a new therapy for others with similar conditions.

New Information

If we receive any new information about the study drug and its side-effects we will inform you.

Alternative Treatments

There are alternative therapies for COPD. Your doctor will discuss the availability and effectiveness of alternative therapies.

Confidentiality

The information collected about you during the study is strictly confidential. For purposes of the study, your medical notes may be made available to the sponsoring company (or representatives) or medical regulatory bodies for the purposes of medical research or for effecting registration of the drug or as may be required in law. If you decide to take part in the study your General Practitioner (GP) will be informed.

Compensation/Costs

If you become ill or injured as a result of participation in this study, medical treatment will be provided, and reasonable costs of such treatment will be met by the sponsoring company. If you have any questions concerning the availability of medical care or if you think you have experienced a research-related injury, contact:

Name: _____ Tel: _____

The sponsoring company will reimburse you for any reasonable additional costs incurred as a participant in this study, i.e. travel expenses to and from the clinic upon presentation of receipts.

What if I Choose Not to Take Part or Want to Stop During the Study

Participation is entirely voluntary. If you decide not to take part you do not need to give any reasons and your medical care will not be affected in any way. You are free to withdraw from the study at any time and do not need to give a reason for doing so.

If you should withdraw from the study, or the doctor has decided it is in your best interest to leave the study, you will be asked about your experience with the study drug and will be asked to have a final medical check. If you withdraw between scheduled visits you will be asked to contact your study doctor to arrange an appointment as soon as possible. You will also be asked to co-operate in having

a laboratory test, a physical examination and to return in 7 days time for a final safety visit.

Questions

You are encouraged to ask questions at any time during the study. If you have a problem or have more questions about the study, please call your doctor as follows:

Contact Name _____

Telephone _____

In case of emergency outside of normal hours or a Gastrointestinal upset:

Contact Name _____

Telephone _____

CONSENT STATEMENT

Study Title: A multicentre, open-label extension study to evaluate the safety, tolerability and efficacy of SB 207499 (15 mg twice daily) in patients with chronic obstructive pulmonary disease (COPD)

Patient Initials _____

Patient Study Number _____

Patient:

I have read the information document and have been given a copy to keep. The study has been explained to me and I have had a chance to ask any questions and all my questions have been answered. I understand that I am free to withdraw from this study at any time without it affecting my medical care. I give consent to the sponsoring company or their representatives to inspect my medical documents for the purposes of the research. By signing this form I give my free and informed consent to take part in this study.

Patient's Signature _____

Patient's Name _____

Date _____

Investigator:

I have fully explained the details of this study to the above named patient. I have explained to the patient his/her freedom to withdraw from the study at any time. I have answered all the questions the patient has at this time and I have offered to answer any future questions. I have informed the patient of whom to contact in the event of a research-related injury. I have provided written information to be taken away by the patient for future reference.

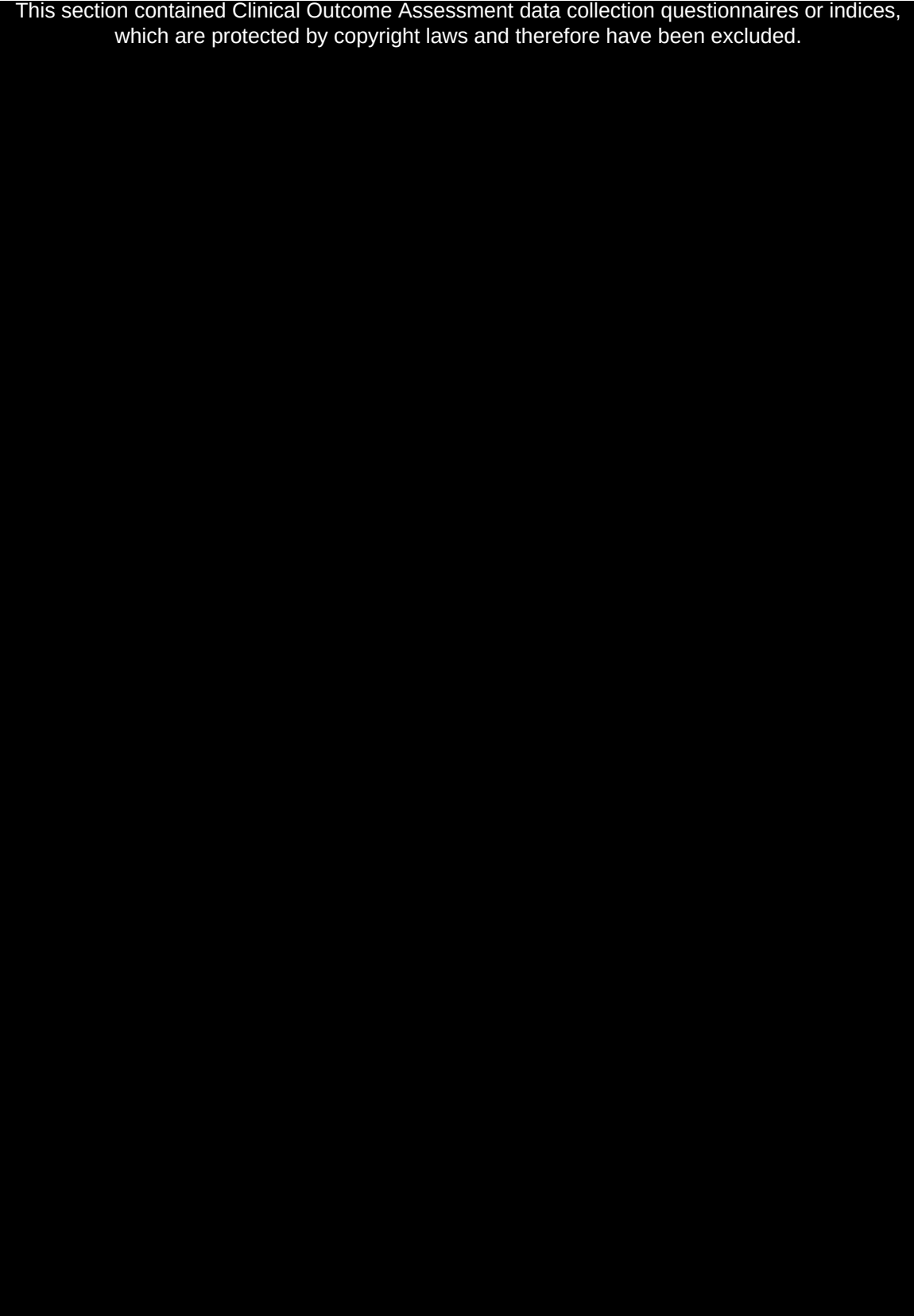
Investigator's Signature _____

Investigator's Name _____

Date _____

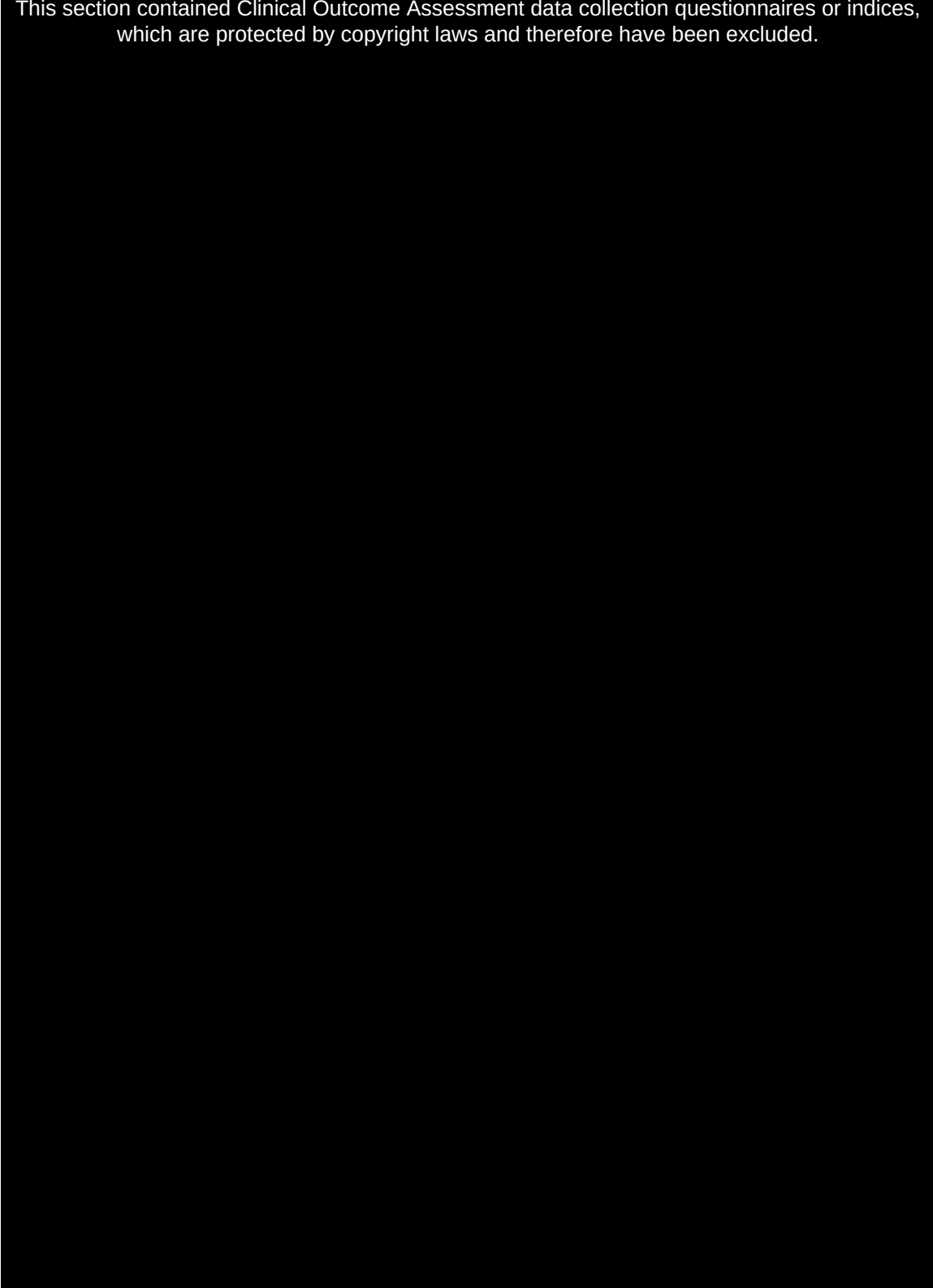
Appendix D: The SF-36 Health Survey Questionnaire

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.



Appendix E: The St George's Respiratory Questionnaire

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.



Appendix F: Gastrointestinal Adverse Experience Monitoring

1. Introduction

Adverse experiences related to the gastrointestinal tract will be closely monitored during this study and gastro-intestinal related symptoms should be recorded on the patient's diary card.

Patients will be instructed to call the Investigator to report any gastrointestinal symptoms which cause them concern or interfere with their daily activities, in particular those which may be associated with acute or chronic gastro-intestinal blood loss such as bloody or black stools, abdominal discomfort pain or cramps and diarrhoea or vomiting. The Investigator must complete a clinical assessment of these gastrointestinal adverse experience(s) within 24 hours of the patient reporting them; he/she should then fax the completed G.I. adverse experience forms to the SB monitor within 24 hours of the clinical assessment.

In order to provide consistent data relating to all of these gastrointestinal adverse experiences, a specific format will be followed for history, physical examination and laboratory assessment of these patients. The format is outlined below and supplied in the CRF. Referral to a gastroenterologist is mandatory if the patient has a positive faecal occult blood test or melaena. (See 2.2 Additional Testing)

2. Assessments of Gastrointestinal Adverse Experiences

2.1 Initial assessment

This assessment will be performed on all patients who report gastrointestinal symptoms which may be associated with acute or chronic gastro-intestinal blood loss such as bloody or black stools, abdominal discomfort pain or cramps and diarrhoea or vomiting. The assessment must include, a history, physical examination and laboratory assessment. Patients who have a positive faecal occult blood test must be referred to a gastroenterologist for a colonoscopy. The following information will be documented in the CRF

History:

The investigator will elicit the history of the symptom with attention to the following features:

Pain; Spatial characteristics; Quality of the pain; Temporal nature of the pain; Does the pain radiate?; Time of onset of gastrointestinal symptom; Time of last dose of study medication.

Physical Examination

- Assessment of general appearance to assess for signs such as jaundice
- Abdominal examination to assess bowel sounds, abdominal tenderness, abdominal masses, and peritoneal signs
- Heart rate and blood pressure, performed while patient is supine followed by sitting with legs dependent, to assess orthostatic changes.

Other significant findings.

Laboratory assessments:

- Faecal occult blood (using a patient collection kit and an investigator analysing kit)
- Urinalysis
- Complete blood count with differential
- Amylase
- Electrolytes
- Blood glucose
- Liver function tests

2.2 Additional Testing

Referral to a gastroenterologist is mandatory if the patient has a positive faecal occult blood test or melaena. The colonoscopy must be **complete** with emphasis on visualisation of the transverse colon and reporting of positive or negative findings, irrespective of other identified pathology or causes for GI bleeding. Biopsies should be taken if appropriate. Results should be faxed to the Sponsor as soon as available.

Additional tests and procedures that may be necessary to diagnose the gastrointestinal adverse experience and/or treat the patient will be performed at the discretion of the Investigator, including, but not limited to, the following:

- Flat plate, upright, decubitus X-ray of abdomen
- Rectal/pelvic examination
- Ultrasound of abdomen
- CT of abdomen
- Stool for ova and parasites
- Other diagnostic tests as deemed necessary by the investigator
- Referral to gastroenterologist, surgeon, or other specialist
- Consider withdrawal for patients with severe or persistent symptoms that may be drug related.

If additional tests are performed, reports should be faxed to the Sponsor as soon as available.

2.3 Daily Follow-up Assessments

Patients who report gastrointestinal adverse experiences which cause them concern or interfere with usual activity will be assessed daily until the adverse experience resolves. Patients can return to the clinic for these evaluations or the Investigator may designate a qualified health care provider to perform the follow-up assessments. These assessments will include an interim history, interim physical examination, and interim laboratory assessment.



SmithKline Beecham

A Multicentre, Open-label Extension Study to Evaluate the Safety, Tolerability and Efficacy of Oral SB 207499 (15 mg twice daily) in Patients with Chronic Obstructive Pulmonary Disease (COPD)

FINAL PROTOCOL (Norway only)

MS**, BSc*, MB BCh MRCP*

*Cardiopulmonary Therapeutic Team, SB, **Biometrics, SB

SB Document Number: SB-207499/RSD-10145X/4

Issue Date:	12 March 1999
Amended:	19 August 1999 (Applicable to Norway only)
Amend 2:	15 November 2000 (not applicable to Norway)
Amend 3:	23 February 2001 (Norway specific – rejected)
Amend 4:	12 April 2001

Endorsements



Clinical Unit: Cardiopulmonary Therapeutic Team

Document No.: SB-207499/RSD-10145X/4

Compound No: SB 207499

Protocol Title: A Multicentre, Open-label Extension Study to Evaluate the Safety, Tolerability and Efficacy of Oral SB 207499 (15 mg twice daily) in Patients with Chronic Obstructive Pulmonary Disease (COPD)

CPMS Number: 207499/040

SB Medical Monitor: Dr [REDACTED]

I, the undersigned, have reviewed this protocol, including Appendices, and I will conduct the clinical study as described and will adhere to the Ethical and Regulatory Considerations stated. I have read and understood the contents of the Investigator Brochure.

Investigator Signature

Date

Print Investigator Name

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List of Abbreviations & Definitions

Abbreviations

AE	adverse experience
ALP	alkaline phosphatase
ALAT (SGPT)	alanine aminotransferase
ASAT (SGOT)	aspartate aminotransferase
bid	twice daily
BP	blood pressure
bpm	beats per minute
BTPS	body temperature and pressure standard
BUN	blood urea nitrogen
cyclic AMP	cyclic adenosine monophosphate
CI	confidence interval
cm	centimetre
COPD	chronic obstructive pulmonary disease
CRF	case report form
DLCO	carbon monoxide diffusing capacity
ECG	electrocardiogram
ERC	ethics review committee
FEF ₂₅₋₇₅	forced expiratory flow at 25-75% vital capacity
FEF ₇₅	forced expiratory flow at 75% vital capacity
FEV ₁	forced expiratory volume in 1 second
FEV ₆	forced expiratory volume in 6 seconds
FVC	forced vital capacity
GCP	good clinical practice
GGT	gamma-glutamyl transferase
hr	hour
HR	heart rate
IRB	institutional review board
IU	international unit
IUD	intrauterine device
kg	kilogram
L	litre
mcg	microgram
mg	milligram
min	minute
mL	millilitre
mmHg	millimetres of mercury
mmol	millimoles
ms	milliseconds

NA	not applicable
ng	nanogram
PDE4	phosphodiesterase 4
PEFR	peak expiratory flow rate
PFT	pulmonary function test
prn	pro re nata (as needed)
R&D	research and development
RBC	red blood cell count
s	second
SB	SmithKline Beecham
SBCL	SmithKline Beecham Clinical Laboratories
SBP	systolic blood pressure
SF-36	short form survey 36
SGRQ	St. George's Hospital Respiratory Questionnaire
SOP	standard operating procedure
uL	microlitre
V	visit
WBC	white blood cell count
WHO	World Health Organisation
wks	weeks

Definitions

adverse experience	includes any noxious, pathologic or unintended change in anatomical, physiologic or metabolic functions as indicated by physical signs, symptoms and/or laboratory changes occurring in any phase of the clinical trial whether or not considered drug related
serious adverse experience	any experience which is fatal, life-threatening, permanently or temporarily disabling or incapacitating or results in hospitalisation, prolongs a hospital stay or is associated with cancer or overdose (either accidental or intentional). In addition, any experience which the Investigator regarded as serious or which suggested any significant hazard, contraindication, side effect or precaution that may have been associated with the use of the drug was reported as serious

Synopsis

Compound/Protocol No.

SB 207499/040

Protocol Title

A multicentre, open-label extension study to evaluate the safety, tolerability and efficacy of oral SB 207499(15 mg twice daily) in patients with chronic obstructive pulmonary disease (COPD).

Rationale

COPD is a disorder characterised by reduced maximum expiratory flow and slow forced emptying of the lungs, features which do not change markedly over several months. It is a major cause of morbidity and mortality. The fixed airflow limitation in COPD is thought to be due to three conditions: chronic bronchitis, emphysema and small airways disease. The airflow obstruction is progressive in nature, mostly irreversible, and may be accompanied by airway hyperreactivity.

The rationale for the use of PDE₄ inhibitors in the treatment of COPD is based upon the role of cyclic adenosine monophosphate (cyclic AMP) as a second messenger that mediates a broad suppression of immune and inflammatory cell activity. SB 207499 has been shown to have marked anti-inflammatory and bronchodilatory activity in multiple *in vitro* and *in vivo* settings. Consequently, PDE₄ inhibitors such as SB 207499 could represent important new treatments for COPD.

In support of the asthma and COPD clinical programs, 13 Phase I studies have been completed to characterise the safety, tolerability, pharmacokinetics and potential drug interaction profile of SB 207499. A total of 1547 patients have been enrolled into eight Phase II clinical trials designed to explore the safety and efficacy of a range of doses of SB 207499. Six studies were conducted in asthmatic patient populations, and two studies in patients with COPD. In COPD study 032, treatment with SB 207499 15 mg bid was clinically and statistically superior to placebo with respect to improvements in pulmonary function parameters. Clinically significant improvements in dyspnoea, beta₂-agonist use

and quality of life were also observed. SB 207499 (repeat dosing up to 15 mg bid) was generally well tolerated in the Phase II program. Headache and nausea were the adverse experiences most commonly associated with treatment with SB 207499, though these events tended to have been reported as mild, and infrequently led to withdrawal. Generally, the onset of nausea has been early during treatment. No obvious effects on laboratory abnormalities, ECGs or vital signs have been observed.

The Phase III COPD program consists of three 6-month randomised, double-blind efficacy and safety trials. Patients completing these studies will have the option of receiving open label medication with SB 207499 (15 mg bid) in one of two extension studies (studies 040 – Europe, South Africa and Australia/New Zealand and 041 – US and Canada). The present study, study 040, is intended to evaluate the long-term safety of SB 207499 (15 mg bid) and to explore the long term efficacy of the compound. Prior to enrolment in study 040, patients must have completed study 042 or study 091 where patients received SB 207499 15 mg bid or placebo for 24 weeks in study 042 and 26 weeks in study 091.

Objective(s)

- To evaluate the long-term safety and tolerability of SB 207499 (15 mg bid) in patients with COPD.
- To further evaluate clinical efficacy of SB 207499 in terms of pulmonary function, disease symptoms and quality of life.

Study Population

The study population will consist of males and females with COPD, who have successfully completed study 042 or study 091 in accordance with the protocol. Approximately 600 patients are expected to be enrolled in the study. Approximately 200 centres within Europe, South Africa and Australia/New Zealand are expected to participate.

Study Design

This study is an open-label extension study, designed to assess the long-term safety, tolerability and efficacy of SB 207499 15 mg bid. This study is open to patients who have completed study 042 or study 091 in accordance with the

protocol (including all assessments at the last double-blind visit). Patients entering the extension study will be required to attend two weekly visits, one biweekly visit and then visits at 4-week intervals during the duration of the study. The study will continue for a period of 96 weeks treatment for patients at centres in Norway. Eligible patients must give written informed consent and meet the additional inclusion/ exclusion criteria for entry into study 040.

There are no restrictions on the use of any concomitant COPD medications (with the exception of theophylline and aminophylline) during this study.

Safety Parameters

- Adverse experiences including additional monitoring for gastrointestinal adverse experiences
- Laboratory safety data
- 12 lead ECG parameters
- Vital signs
- Physical examination including respiratory examination

Efficacy Parameters

- Pulmonary function tests (FEV₁, FEV₆, FEF₂₅₋₇₅, FEF₇₅, FVC, PEF_R)
- Exercise tolerance test (6-minute walk test)
- Dyspnoea assessments (modified Borg scale) at rest to assess overall dyspnoea since the last visit and after exercise tolerance test
- COPD exacerbation rates
- Quality of life assessments
- Healthcare utilisation

Study Procedure

Patients will be assessed for their eligibility for study 040 at their final scheduled visit (prior to Safety Follow-up visit) in study 042 or study 091. Eligible patients will receive SB 207499 at a dose of 15 mg bid for the duration of the study. The study blind from the previous study will not be broken before entering patients into study 040. With the exception of theophylline or aminophylline (oral or intravenous) other COPD medication is permitted to be used concomitantly with SB 207499.

Assessment Schedule:

Safety: Adverse experiences, resting 12-lead ECG parameters, vital signs and laboratory tests will be recorded at every visit. Additional monitoring for gastrointestinal adverse experiences will be measured at 24 weeks, 48 weeks and 96 weeks.

Efficacy: Pulmonary function tests will be measured at every visit except Visit 2. COPD exacerbation assessment and healthcare utilisation will be recorded at every visit. Overall breathlessness (modified Borg) will be performed at every visit except Visit 2. Exercise tolerance test (6-minute walk) will be performed at Visits 1, 6, 9, 12 and 15 and then every 12 weeks. Quality of life assessments (SGRQ and SF-36) will be recorded at Visits 1, 9 and 15 and then every 24 weeks (An additional SGRQ assessment will be performed at Visit 6).

Statistical Evaluation

This is a phase III open-label trial with the primary purpose of evaluating patient safety. No formal power calculations were performed.

Descriptive statistics including 95% confidence intervals will be provided for the change from baseline of each serially collected efficacy parameter. Baseline will be defined as the predose assessment at the randomisation visit of the parent studies, 042 and 091. For patients randomised to placebo in study 042 or study 091 additional analyses will be performed based on the change from the final assessments prior to dosing in study 040.

All efficacy analyses will be based on the population of patients receiving at least one dose of study medication and having an assessment of efficacy in the study.

Safety analyses will be based on all patients receiving at least one dose of study medication. Summaries of adverse experiences, ECGs, vital signs, and clinical laboratories will be provided.

1.0 Introduction

SB 207499 is a potent and selective phosphodiesterase type 4 (PDE₄) inhibitor currently under development for the treatment of asthma and chronic obstructive pulmonary disease (COPD).

COPD is a disorder characterised by reduced maximum expiratory flow and slow forced emptying of the lungs, features which do not change markedly over several months. [2] It is a major cause of morbidity and mortality. The fixed airflow limitation in COPD is thought to be due to three conditions: chronic bronchitis, emphysema and small airways disease. The airflow obstruction is progressive in nature, mostly irreversible, and may be accompanied by airway hyperreactivity. [1]

Tobacco smoking is the major cause of COPD, so cessation of smoking is important in the prevention and treatment of COPD. Current therapy (e.g., bronchodilators) treats the symptoms of COPD and not the actual condition.

The rationale for the use of PDE₄ inhibitors in the treatment of COPD is based upon the role of cyclic adenosine monophosphate (cyclic AMP) as a second messenger that mediates a broad suppression of immune and inflammatory cell activity. SB 207499 has been shown to have marked anti-inflammatory and bronchodilatory activity in multiple *in vitro* and *in vivo* settings. Consequently, PDE₄ inhibitors such as SB 207499 could represent important new treatments for COPD.

In support of the asthma and COPD clinical programs, 13 Phase I studies have been completed to characterise the safety, tolerability, pharmacokinetics and potential drug interaction profile of SB 207499. A total of 1547 patients have been enrolled into eight Phase II clinical trials designed to explore the safety and efficacy of a range of doses of SB 207499. Six studies were conducted in asthmatic patient populations and two studies in patients with COPD.

The Phase II COPD clinical program consisted of studies 032 and 038, conducted in Europe and the US, respectively. The study design and entry criteria for both studies were standardised. COPD was defined by International Treatment Guidelines and entry criteria were established to ensure that patients had COPD rather than asthma. Both studies 032 and 038 were multicentre, double-blind, placebo-controlled, dose-ranging trials. Study 032 was of six weeks duration and evaluated SB 207499 dosages of 5, 10 and 15 mg bid. Study 038 investigated

lower doses of 2.5 and 5 mg bid for four weeks. In both studies, the primary efficacy endpoint was clinic trough FEV₁. The results of study 032 demonstrated significant and clinically relevant efficacy of SB 207499 at 15 mg bid. SB 207499 15 mg bid was significantly superior to placebo with respect to improvements in pulmonary function parameters (FEV₁, FVC and PEF_R). Superiority was substantiated by positive trends in symptoms (dyspnoea) and a reduction in beta₂-agonist use.

Administration of SB 207499 to healthy volunteers at dosages up to and including 15 mg bid has been well tolerated and has not raised any safety concerns. Adverse experiences in the Phase I studies have, in general, been mild to moderate, with nausea and headache as the most commonly reported events. SB 207499 (repeat dosing up to 15 mg bid) was generally well tolerated in the Phase II program. There is no evidence of any adverse effect on laboratory parameters, vital sign values, or electrocardiographic parameters. Headache and nausea were the adverse experiences most commonly associated with treatment with SB 207499, though these events tended to be mild, and infrequently led to withdrawal. The gastrointestinal adverse experiences typically occurred early during treatment, resolved on therapy during the study, and tended not to recur.

The Phase III COPD program consists of three 6-month randomised, double-blind efficacy and safety trials. Patients completing these studies will have the option of receiving open label medication with SB 207499 (15 mg bid) in one of two extension studies (studies 040 – Europe, South Africa and Australia/New Zealand and 041 – US and Canada). The present study, study 040, is intended to evaluate the long-term safety of SB 207499 (15 mg bid) and to explore the long term efficacy of the compound. Prior to enrolment in study 040, patients must have completed study 042 or study 091 where patients received SB 207499 15 mg bid or placebo for 24 weeks in study 042 and 26 weeks in study 091.

2.0 Objectives

2.1 Primary Objective

The primary objective of this study is to evaluate the long-term safety and tolerability of SB 207499 administered at a dosage of 15 mg bid in patients with COPD.

2.2 Secondary Objective

The secondary objective of this study is to evaluate further the efficacy of SB 207499 in terms of pulmonary function, disease symptoms and quality of life.

3.0 Study Design Overview and Flow Chart

This is a multicentre, Phase III, open-label extension study in patients with COPD. The study will continue for a period of 96 weeks treatment for patients at centres in Norway.

Patients who have previously completed study 042 or study 091 must satisfy additional inclusion and exclusion criteria (Sections 4.2 and 4.3) before beginning Protocol 040 at a dosage of SB 207499 of 15 mg bid. Patients will be assessed for their eligibility for study 040 at their final scheduled visit of study 042 at Week 24, or study 091 at Week 26 (i.e. prior to Safety Follow-up visit). The study blind from the previous studies will not be broken before entering into study 040.

During the treatment period, patients will attend the clinic after one, two, and four weeks and then at four-week intervals (Figure 1), and the assessments specified in Table 1 and in Section 5.3 will be made. Patients will return for a follow-up visit one to two weeks after the last visit on open-label treatment.

On non-visit days, study medication will be taken orally, twice daily, in the morning *after* breakfast and in the evening *after* a meal. **Note:** Patients entering study 040 from study 042 will take the final dose of study 042 medication in clinic prior to entering study 040 and will take first dose of 040 study medication after their evening meal allowing at least 8 hours since the time of the last dose of study medication taken in the clinic. On visit days, patients will refrain from taking the morning dose of study medication before their clinic visit.

All other COPD medications (with the exception of theophylline and aminophylline (oral and intravenous)) will be permitted without restriction for all patients in Protocol 040.

Figure 1: Study Design

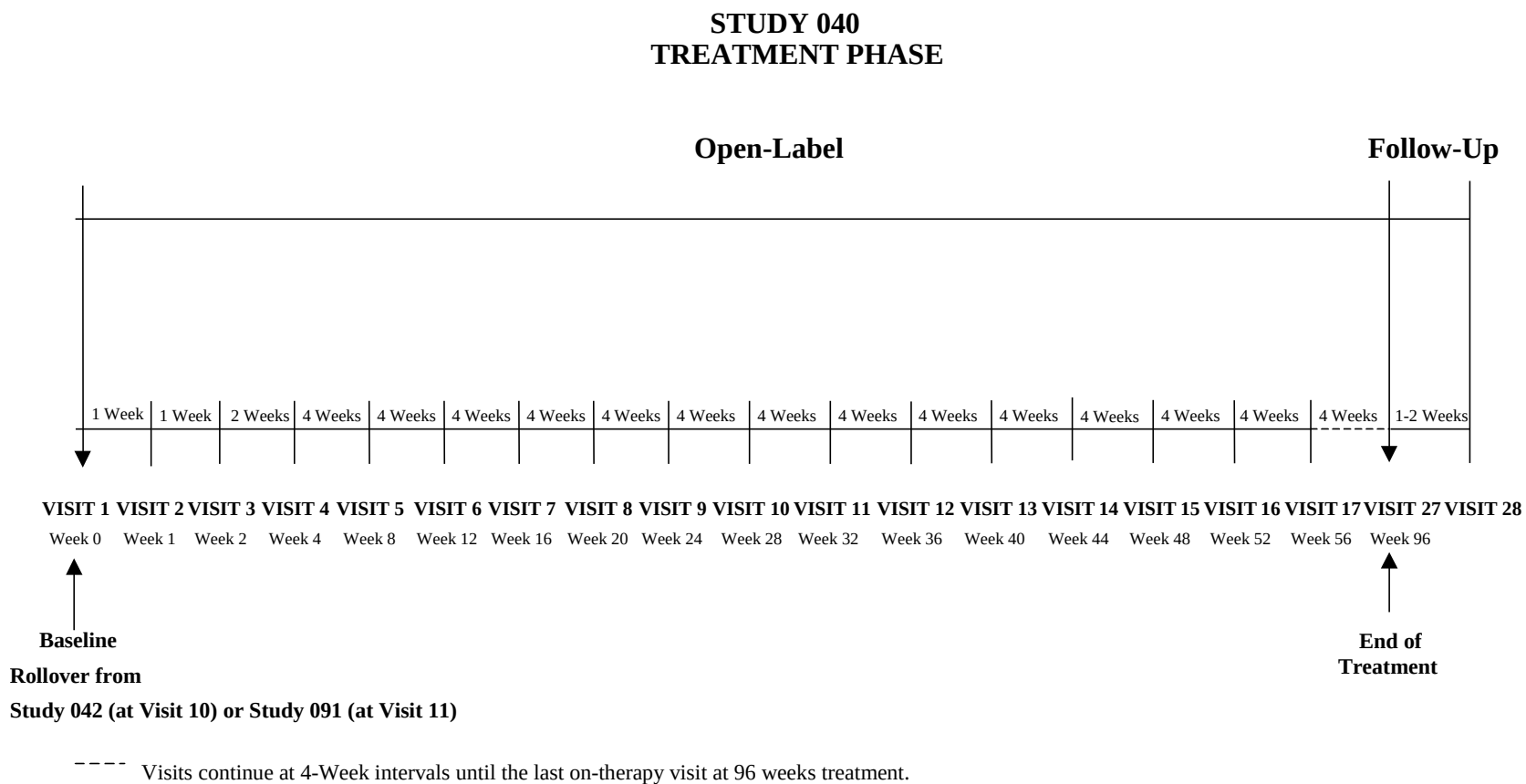


Table 1 Outline of Study Procedures

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16		
Time relative to baseline (weeks)	Baseline 0	+1	+2	4	8	12	16	20	24	28	32	36	40	44	48	52	Early Withdrawal	Follow-up Final Visit +1 week
Signed written informed consent	x																	
Study medication compliance		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant medication	x ¹	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Diary card review ⁷		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse experiences ⁸	x ¹	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
COPD exacerbation assessment/ healthcare utilisation	x ¹	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical (including respiratory) examination	x ¹								x						x ^{**}		x	x ²
Resting 12-lead ECG	x ¹	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x ²
Vital signs (BP, HR) ³	x ¹	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Overall Breathlessness (modified Borg)	x ¹		x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Exercise tolerance test (6-minute walk)	x ¹					x			x			x			x [*]			
Post-exercise breathlessness	x ¹					x			x			x			x [*]			
Pulmonary function tests ⁴	x ¹		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Laboratory tests ⁵	x ¹	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x ²
Pregnancy test ⁶	x ¹			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Quality of life assessments: SGRQ	x ¹					x			x						x ^{**}		x	
Quality of life assessments: SF-36	x ¹								x						x ^{**}		x	
Dispense or re-dispense open-label medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Study conclusion record																	x	

- 1 Assessed during Visit 10, final double-blind visit, of Study 042 and visit 11 of Study 91 (except the QoL assessments for study 091 which are performed at visit 10)
- 2 Only if abnormalities are present at the previous visit
- 3 Orthostatic blood pressure and heart rate are measured at 24 weeks, 48 weeks and 96 weeks. Also at Early Withdrawal
- 4 To include FEV₁, FEV₆, FVC, FEF₂₅₋₇₅, FEF₇₅, and PEF_R
- 5 Faecal occult blood is measured at 24 weeks, 48 weeks and 96 weeks. Also at Early Withdrawal. Baseline measure is taken from last FOB in study 042 or study 091.
- 6 Serum pregnancy test for female patients of child bearing potential. Urine test only is done at Follow-up Visit.
- 7 A Diary Card is issued at each visit. The patient will use the Diary Card to record if they feel differently since the previous visit
- 8 Patients will be assessed for GI AEs at every visit
- * Measured every 12 weeks thereafter
- ** Measured every 24 weeks thereafter

4.0 Study Population

4.1 Number of Patients

It is anticipated that approximately 600 patients will be entered in the study. Approximately 200 centres within Europe, South Africa and Australia/New Zealand are to participate.

4.2 Inclusion Criteria

Patients who fulfil the following criteria will be eligible for inclusion in the study.

- 1 Males or females with COPD who have successfully completed study 042 or study 091 where patients received SB 207499 15 mg bid or placebo for 24 weeks in study 042 and 26 weeks in study 091 without tolerability problems.

Note: Women of childbearing potential must be using effective contraceptive measures (i.e., oral contraceptives, Norplant[®], an IUD, a diaphragm with spermicide, a condom with spermicide, or Depo-Provera[®]) prior to Visit 1 and must continue using the same contraceptive measure during the study.

- 2 Patients who have given their written informed consent to participate.

4.3 Exclusion Criteria

The following patients are not eligible for inclusion into the study.

- 1 Women who are pregnant or lactating, or who plan for pregnancy within the next 24 months
- 2 Patients who withdrew from study 042 or study 091 for any reason
- 3 Patients with a positive faecal occult blood test between Weeks 20 and 24 in study 042 and study 091
- 4 Patients who experienced a serious adverse experience, a gastrointestinal adverse experience or a clinically significant laboratory abnormality, which in the opinion of the Investigator could have been attributed to study medication, during study 042 or study 091 and which was still present at the end of either study.

- 5 Patients who in the opinion of the Investigator are not suitable for enrolment into the study.

5.0 Conduct of the Study

5.1 Ethics and Regulatory Considerations

The study will be conducted according to Good Clinical Practice, the World Medical Association Declaration of Helsinki ([Appendix A](#)).

5.1.1 Ethics Review Committee/Institutional Review Board

Ethics Review Committees (ERCs)/Institutional Review Boards (IRBs) must be constituted according to the local laws/customs of each participating country.

This protocol will be submitted to an appropriate committee or board and its written unconditional approval obtained and submitted to the sponsor before the study is begun. SmithKline Beecham (SB) will supply the Investigator with relevant data for submission to the hospital/university/independent ERC/IRB for the review and approval of the protocol. Verification of the ERC/IRB's unconditional approval of the protocol and the written informed consent statement will be transmitted to the SB study monitor prior to shipment of drug supplies and case report forms (CRFs) to the site. This approval must refer to the study by exact protocol title and number, identify the documents reviewed, and state the date of review.

The ERC/IRB must be informed by the Investigator of all subsequent protocol amendments and of serious or unexpected adverse experiences occurring during the study that are likely to affect the safety of the subjects or the conduct of the study. Approval for such changes must be transmitted in writing to the SB study monitor via the Investigator.

5.1.2 Informed Consent

The principles of informed consent in the current edition of the World Medical Association Declaration of Helsinki ([Appendix A](#)) should be implemented in each clinical study before protocol-specified procedures are carried out.

Information should be given in both oral and written form whenever possible and deemed appropriate by the ERC/IRB. Subjects and their relatives, guardians, or if necessary, legal representatives must be given ample opportunity to inquire about details of the study.

The consent form generated by the Investigator with the assistance of SB, must be approved (along with the protocol) by the ERC/IRB and be acceptable to SB. Consent forms must be in a language fully comprehensible to the prospective subject. Where appropriate, informed consent shall be documented by the use of a written consent form approved by the ERC/IRB and signed by the subject or the subject's legally authorised representative. The written consent document will embody the elements of informed consent as described in the World Medical Association Declaration of Helsinki and will also comply with local regulations. This form may be read to the subject or the subject's legally authorised representative, but, in any event, the Investigator shall give either the subject or the representative adequate opportunity to read it before it is signed.

Consent must be documented either by the subject's dated signature or by the signature of an independent witness who records the subject's assent. In either event, the signature confirms that the consent is based on information that has been understood. Each subject's signed informed consent form must be kept on file by the Investigator for possible inspection by regulatory authorities and/or SB professional and regulatory compliance personnel.

A sample informed consent is provided in [Appendix C](#).

5.2 General Instructions

5.2.1 Study Visits

For each scheduled study visit, patients will be required to attend the clinic in the morning, at about the same time of day (preferably 10:00 ± 2 hours), not having taken the morning dose of study medication, and having refrained from using beta₂-agonists (short-acting), anticholinergic medications and smoking during the two-hour period and from using beta₂-agonists (long-acting) during the 12-hour period preceding the visit.

Smoking and the use of beta₂-agonists or anticholinergic treatment must be avoided during the clinic stay if at all possible. Patients must **not** take their morning doses of study medication before attending morning clinic visits.

In exceptional circumstances, a patient may be allowed afternoon appointments only if **≥ 8 hours have elapsed** since the last dose of study medication and the Investigator is capable of completing all visit assessments. This will ensure that trough measurements are obtained. For example, if the morning dose of study medication is taken after breakfast at 8:00 a.m., the patient's appointment may be scheduled after 4:00 p.m. the same day. If an afternoon visit is scheduled, patients should be instructed to take the morning dose of study medication after breakfast, which must be at least 8 hours before their clinic visit.

5.2.2 Assignment of Patient Identification Numbers

The patient number assigned to each patient during study 042 or study 091 will be used for that patient during Protocol 040.

5.3 Study Sequence

Patients completing study 042 or study 091 will enter study 040 at their final "On-therapy" visit (i.e. Visit 10 for study 042 and Visit 11 for study 091). **There should be no gap between completing the preceding study and entering study 040.**

5.3.1 Week 0, Visit 1

Data from Visit 10 (Week 24) of study 042 or Visit 11 (week 26) of study 091 will provide the Visit 1 data, including:

- Quality of life assessments – SGRQ and SF-36 (Section 7.3). (This assessment is performed at visit 10 for patients in study 091.)
- Concomitant medication
- Adverse experiences
- COPD exacerbation assessment and healthcare utilisation assessment (Sections 7.1, 7.2 and 8.1.1)
- Physical examination, including a respiratory examination (Section 5.4.1)
- Smoking status and Pulmonary Rehabilitation Programme status
- Sitting blood pressure and heart rate; orthostatic blood pressure and heart rate (Section 5.4.1)
- Resting 12-lead ECG (Section 5.4.2)
- Blood and urine samples for routine haematology, biochemistry and urinalysis (pregnancy testing for females of childbearing potential) (Section 5.4.3)
- Pulmonary function tests (Section 5.4.5)
- Exercise tolerance test (6-minute walk test) (Section 5.4.6).
- Overall breathlessness assessment (Borg scale) (Section 5.4.7)
- Post-exercise breathlessness (Section 5.4.7)

Note: Any assessments that were not performed at the Visit 10 or Visit 11 of study 042 and 091, will be performed at this visit.

A checklist of the inclusion and exclusion criteria (Sections 4.2 and 4.3) will be completed and written informed consent obtained. If the patient is eligible to enter study 040, the patient's identification number (PID) from study 042 or study 091 will be copied onto the CRF and the following should be performed:

- Issue one bottle (a 35-day supply) of open-label study medication.

Patients entering study 040 from study 091 will take the first dose from the new bottle of study medication in the clinic with food, and patients will be reminded to take the first evening dose of medication after their evening meal (at approximately 20:00).

Patients entering study 040 from study 042 will take the first dose from the new bottle of study medication after their evening meal allowing at least 8 hours since the time of the last dose of study medication taken in the clinic.

- Issue a diary card which will be used by the patient to record if they feel differently since starting the study. A diary card will be issued at each visit.
- Review the procedure for reporting gastrointestinal adverse experiences with the patient (Section 8.1.2).

Patients will be instructed to return to the clinic within 7 (± 2) days for the Week 1 visit (Visit 2) and reminded:

- Not to take the morning dose of SB 207499 on the morning of the Week 1 visit (Visit 2) if a morning appointment is scheduled
- To refrain from taking beta₂-agonists (short-acting) or anticholinergic medications for two hours and beta₂-agonist (long-acting) for 12 hours before the next visit.
- To refrain from smoking for two hours immediately preceding the Week 1 visit (Visit 2)
- To bring all empty medication bottles and any remaining study medication to the next clinic visit.

5.3.2 End of Week 1 (Visit 2)

At the end of Week 1, the following procedures will be completed:

- Document if the patient has taken inhaled beta₂-agonists (short-acting), anticholinergic medication, or smoked during the two-hour period or beta₂-agonists (long-acting) during the 12-hour period preceding the visit.
- The diary card will be collected and reviewed (Section 5.4.4). Any adverse experiences which have occurred will be recorded in the CRF and followed-up as necessary (Section 8.0).
- Compliance in taking study medication will be determined (Section 6.9). The Investigator will emphasise the importance of compliance to patients with compliance <80% or >120%.
- Any changes or additions to the patient's concomitant medication and any additions to medical procedures will be recorded in the CRF (Section 6.4). Smoking status will also be documented.
- Determine if the patient has entered a Pulmonary Rehabilitation Programme since the last visit.
- A COPD exacerbation assessment will be made to determine if the patient has experienced any exacerbations since the last visit (Section 8.1.1).
- A healthcare utilisation assessment will be performed (Sections 7.1 and 7.2).
- Blood and urine samples will be obtained for routine haematology, biochemistry and urinalysis (Section 5.4.3).

Greater than 2 hours after the patient's last short-acting beta₂-agonist or greater than 12 hours after the last long-acting beta₂-agonist:

- A 12-lead electrocardiogram will be performed after the patient has been semisupine for 5 minutes (Section 5.4.2).
- Blood pressure and heart rate will be measured after 5 minutes in a sitting position (Section 5.4.1).

Patients who withdraw from the study during the visit should complete all scheduled visit assessments along with pulmonary function tests, the SGRQ and SF-36 questionnaires, a physical examination, assessments of orthostatic changes in blood pressure and heart rate and faecal occult blood (Section 5.3.8).

For patients continuing in the study:

- **Reissue the bottle of study medication dispensed at Visit 1.** The next dose of study medication will be administered in the clinic with food.

- Issue a new diary card. The patient should be reminded to use the card to record if they feel differently since starting the study.
- Review reporting requirements for gastrointestinal symptoms (Section 8.1.2).

Patients will be instructed to return to the clinic for the Week 2 visit (Visit 3) in 7 (± 2) days. Patients will also be reminded:

- to take the evening dose immediately after the evening meal.
- **not** to take the morning dose of study medication at home on the morning of the next clinic visit if a morning appointment is scheduled.
- to refrain from taking beta₂-agonists (short-acting) or anticholinergic medications for two hours and beta₂-agonists (long-acting) for 12 hours before the next visit.
- to refrain from smoking for two hours immediately preceding the next visit.
- to bring any remaining study medication tablets, all study medication containers, and diary card with them to the next visit.

5.3.3 End of Week 2 (Visit 3)

At the end of Week 2, the following procedures will be completed:

- Document if the patient has taken inhaled beta₂-agonists (short-acting), anticholinergic medication, or smoked during the two-hour period or beta₂-agonists (long-acting) during the 12-hour period preceding the visit.
- The diary card will be collected and reviewed (Section 5.4.4). Any adverse experiences which have occurred will be recorded in the CRF and followed-up as necessary (Section 8.0).
- Compliance in taking study medication will be determined (Section 6.9).
- Any changes or additions to the patient's concomitant medication and any additional medical procedures will be recorded in the CRF (Section 6.4). Any changes in smoking status will also be documented.
- Determine if the patient has entered a Pulmonary Rehabilitation Programme since the last visit.
- A COPD exacerbation assessment will be made to determine if the patient has experienced any exacerbations since the last visit (Section 8.1.1).

- A healthcare utilisation assessment will be performed (Sections 7.1 and 7.2).
- Overall breathlessness will be assessed using the modified Borg scale (Section 5.4.7).

To continue in the study, patients must show **>80% or < 120%** compliance in taking study medication at two consecutive visits. Patients who do not meet this criterion must be withdrawn from the study.

The following assessments will be made:

- Blood and urine samples will be obtained for routine haematology, biochemistry and urinalysis (Section 5.4.3).

Greater than 2 hours after the patient's last short-acting beta₂-agonist or greater than 12 hours after the last long-acting beta₂-agonist:

- A 12-lead electrocardiogram will be performed after the patient has been semisupine for 5 minutes (Section 5.4.2).
- Blood pressure and heart rate will be measured after 5 minutes in a sitting position (Section 5.4.1).
- Pulmonary function tests will be performed before administration of the next dose of study medication in the clinic (Section 5.4.5). **Note: If the patient has taken short acting beta₂-agonists or anticholinergic medication during the 2 hours prior to the visit, a 2-hour period should elapse before pulmonary function tests are performed. If the patient has taken long-acting beta₂-agonists during the 12 hours prior to the visit, a total of 12 hours must elapse before pulmonary function tests are performed.**

Patients who withdraw from the study during the visit should complete all scheduled visit assessments, the SGRQ and SF-36 questionnaires, a physical examination, assessments of orthostatic changes in blood pressure and heart rate and faecal occult blood (Section 5.3.8).

For patients who are continuing in the study:

- **Reissue the bottle of study medication dispensed at Visit 1.** The next morning dose of study medication will be administered in the clinic with food.
- Issue a new diary card. The patient should be reminded to use the card to record if they feel differently since starting the study.
- Review the procedure for reporting gastrointestinal adverse experiences with the patient.

Patients will be asked to return to the clinic in the morning in 14 ($\pm$ 3) days for the Week 4 visit (Visit 4). They will also be reminded:

- to take the next dose immediately after the evening meal.
- **not** to take the morning dose of study medication at home on the morning of their next clinic visit if a morning appointment is scheduled.
- To refrain from taking beta₂-agonists (short-acting) or anticholinergic medications for two hours and beta₂-agonists (long-acting) for 12 hours before the next visit.
- to refrain from smoking for 2 hours immediately preceding the next visit.
- to bring any remaining study medication tablets, all study medication containers, and the diary card with them to the next visit.

5.3.4 Visits at 4-Week Intervals (Weeks 4, 8, 12, 16, 20, 24, 28, etc; Visits 4, 5, 6, 7, 8, 9, 10, etc.)

At the end of every 4-week interval, the following will be performed:

- Document if the patient has taken inhaled beta₂-agonists (short-acting), anticholinergic medication, or smoked during the two-hour period or beta₂-agonists (long-acting) during the 12-hour period preceding the visit.
- The diary card will be collected and reviewed (Section 5.4.4). Any adverse experiences which have occurred will be recorded in the CRF and followed-up as necessary (Section 8.0).
- Compliance in taking study medication will be determined (Section 6.9). Any medication remaining in the returned bottle will be retained by the Investigator.
- Any changes or additions to the patient's concomitant medication and any additions to medical procedures will be recorded in the CRF (Section 6.4). Smoking status will also be documented.
- Determine if the patient has entered a Pulmonary Rehabilitation Program since the last visit.
- A COPD exacerbation assessment will be made to determine if the patient has experienced any exacerbations since the last visit (Section 8.1.1).
- A healthcare utilisation assessment will be performed (Sections 7.1 and 7.2).

- Overall breathlessness will be assessed using the modified Borg scale (Section 5.4.7).

To continue in the study, patients must show > **80% or** < **120%** compliance in taking study medication at two consecutive visits. Patients who do not meet this criterion must be withdrawn from the study.

The following assessments will be made:

- Blood and urine samples will be obtained for routine haematology, biochemistry (including beta-HCG for women of childbearing potential) and urinalysis (Section 5.4.3).

Greater than 2 hours after the patient's last short-acting beta₂-agonist or greater than 12 hours after the last long-acting beta₂-agonist:

- A 12-lead electrocardiogram will be performed after the patient has been semisupine for 5 minutes (Section 5.4.2).
- Blood pressure and heart rate will be measured after 5 minutes in a sitting position (Section 5.4.1).
- Pulmonary function tests will be performed before administration of the next dose of study medication in the clinic (Section 5.4.5). **Note: If the patient has taken short acting beta₂-agonists or anticholinergic medication during the 2 hours prior to the visit, a 2-hour period should elapse before pulmonary function tests are performed. If the patient has taken long-acting beta₂-agonists during the 12 hours prior to the visit, a total of 12 hours must elapse before pulmonary function tests are performed.**

Patients who withdraw from the study during the visit should complete all scheduled visit assessments. In addition, the SGRQ and SF-36 questionnaires, a physical examination, assessments of orthostatic changes in blood pressure and heart rate and faecal occult blood tests should be completed if not performed at that visit (Section 5.3.8).

For patients who are continuing in the study:

- Issue one bottle (a 35-day supply) of study medication. The next morning dose of study medication will be administered in the clinic with food.
- A new diary card will be issued. The patient will be reminded to use the card to record if they feel differently since starting the study.

- Review the procedure for reporting gastrointestinal adverse experiences with the patient.

Patients will be asked to return to the clinic at the same time of day in 28 ($\pm$ 6) days for their next visit. They will also be reminded:

- to take the next dose immediately after the evening meal.
- **not** to take the morning dose of study medication at home on the day of their next clinic visit if a morning appointment is scheduled.
- to refrain from taking beta₂-agonists (short-acting) or anticholinergic medications for two hours and beta₂-agonists (long-acting) for 12 hours immediately preceding the next visit.
- to refrain from smoking for 2 hours immediately preceding the next visit.
- to bring with them any remaining study medication tablets, all study medication containers, and the diary cards.

5.3.5 Visits at 12-Week Intervals (Weeks 12, 24, 36, 48, 60, 72, 84, 96; Visits 6, 9, 12, 15, 18, 21, 24, 27)

In addition to the procedures which will be performed at 4-week intervals (Section 5.3.4), the following assessments will occur at 12-week intervals:

Greater than 2 hours after the patient's last short-acting beta₂-agonist or greater than 12 hours after the last long-acting beta₂-agonist:

- An exercise tolerance test (6-minute walk) will be completed (Section 5.4.6).
- Breathlessness using the modified Borg scale, will be assessed immediately after the exercise tolerance test (Section 5.4.7).

Note: At least 10 minutes should elapse between the exercise tolerance test and pulmonary function testing so that the patient is fully rested during their pulmonary function tests.

For patients attending visits at 12-weekly intervals:

Issue a 105- day supply of study medication: either three bottles containing 70 tablets, or one bottle containing 210 tablets.

Patients will be asked to return to the clinic at the same time of day in 84 ($\pm$ 6) days for their next visit.

5.3.6 Visits at 24-Week Intervals (Weeks 24, 48, 72 and 96; Visits 9, 15, 21 and 27)

At the end of Weeks 24, 48, 72 and 96, the assessments described for the 4- and 12 -week intervals will be performed (Sections 5.3.4 and 5.3.5). The following evaluations will also be performed:

- Quality of life questionnaires, the SGRQ and the SF-36, will be administered before any other assessments (Section 7.3, Appendices E and F).
- Physical examination, including respiratory examination (Section 5.4.1).
- Orthostatic blood pressure and heart rate will be measured after 5 minutes in a supine position followed by sitting with legs dependent for 1 minute (Section 5.4.1). **Orthostatic measures will be made at 24 weeks and 48 weeks and annually thereafter.**
- Patients will be issued a faecal occult blood kit and instructed to follow the instructions on the kit (Section 5.4.3). **Faecal occult blood will be assessed at 24 weeks and 48 weeks and annually thereafter.**

All of these assessments will be performed at the last on-therapy visit for all patients.

5.3.7 Safety Follow-up Visit

A Follow-up visit will be required one week after the last visit on open-label treatment. At this visit, the Investigator will:

- Document if the patient has taken inhaled beta₂-agonists (short-acting), anticholinergic medication, or smoked during the two-hour period or beta₂-agonists (long-acting) during the 12-hour period preceding the visit.
- Record in the CRF and follow up, as appropriate, any adverse experiences that have occurred (Section 8.0)
- Record in the CRF any changes or additions to patient's concomitant medications and any additional medical procedures. Smoking status will also be documented.
- Determine if the patient has entered a Pulmonary Rehabilitation Program since the last visit.
- Perform a COPD exacerbation assessment and healthcare utilisation assessment (Sections 7.1, 7.2 and 8.1.1).

The following assessments will also be made:

- A physical examination, including a respiratory examination, will be performed if abnormal findings were observed at the last visit (Section 5.4.1)
- Blood and urine samples will be obtained for routine haematology and biochemistry and urinalysis only if abnormal findings were observed at the last visit (Section 5.4.3)
- A urine pregnancy test will be performed for all women of child-bearing potential (Section 5.4.3).

Greater than 2 hours after the patient's last short-acting beta₂-agonist or greater than 12 hours after the last long-acting beta₂-agonist:

- Sitting blood pressure and heart rate (Section 5.4.1)
- A 12-lead electrocardiogram will be performed after the patient has been semisupine for 5 minutes if abnormal findings were observed at the last visit (Section 5.4.2)
- Pulmonary function tests (Section 5.4.5). **Note: If the patient has taken short acting beta₂-agonists or anticholinergic medication during the 2 hours prior to the visit, a 2-hour period should elapse before pulmonary function tests are performed. If the patient has taken long-acting beta₂-agonists during the 12 hours prior to the visit, a total of 12 hours must elapse before pulmonary function tests are performed.**

5.3.8 Early Withdrawal

Early withdrawal assessments and procedures should be completed for all patients who withdraw or are withdrawn from the study after receiving open-label treatment, but prior to the end of the open-label treatment phase, and also at Visit 27 (Week 96) for all patients completing the study. For patients who withdraw or are withdrawn at a scheduled visit, the assessments and procedures will be performed at that visit. Patients who withdraw or are withdrawn between scheduled visits should have an early withdrawal visit scheduled within 24 hours after discontinuation of study medication. If patients are unable to return within 24 hours they will be asked to return in 7 ($\pm$ 3) days for a safety follow-up visit. The following assessments and procedures will be performed at the early withdrawal visit:

- Quality of life questionnaires, the SGRQ and the SF-36, will be administered before any other assessments (Section 7.3, Appendices E and F)

- Review patient diary (Section 5.4.4) and record in the CRF and follow up, as appropriate, any adverse experiences that have occurred (Section 8.0)
- Compliance in taking study medication will be determined (Section 6.9).
- Record in the CRF any changes or additions to patient's concomitant medications and any additional medical procedures. Smoking status will also be documented.
- Determine if the patient has entered a Pulmonary Rehabilitation Program since the last visit.
- Perform a COPD exacerbation assessment and healthcare utilisation assessment (Sections 7.1, 7.2 and 8.1.1)
- Physical examination, including a respiratory examination (Section 5.4.1)
- Blood and urine samples for routine haematology, biochemistry and urinalysis (pregnancy testing for females of childbearing potential) (Section 5.4.3)
- Patients will be issued faecal occult blood kit (Section 5.4.3)

Greater than 2 hours after the patient's last short-acting beta₂-agonist or greater than 12 hours after the last long-acting beta₂-agonist:

- Sitting blood pressure and heart rate; orthostatic blood pressure and heart rate (Section 5.4.1)
- Resting 12-lead ECG (Section 5.4.2)
- Pulmonary function tests (Section 5.4.5). **Note: If the patient has taken short acting beta₂-agonists or anticholinergic medication during the 2 hours prior to the visit, a 2-hour period should elapse before pulmonary function tests are performed. If the patient has taken long-acting beta₂-agonists during the 12 hours prior to the visit, a total of 12 hours must elapse before pulmonary function tests are performed.**
- Study conclusion record.

5.4 Clinical Observations and Procedures

5.4.1 Physical Examination and Respiratory Examination (24-week Intervals) and Vital Signs (All Visits)

At each 24-week interval, at early withdrawal and at the Follow-up visit (if abnormal at the previous visit), the Investigator will answer the following question "Has there been a clinically significant worsening since the last assessment in the patient's physical condition?" A specific respiratory examination will also be made. All significant findings will be recorded in the CRF.

Greater than 2 hours after the patient's last short-acting beta2-agonist or greater than 12 hours after the last long-acting beta2-agonist administration, vital signs (blood pressure and heart rate) will be measured at all visits after the patient has been sitting for at least five minutes.

At Weeks 24, 48 and 96; at early withdrawal and at visits associated with gastrointestinal adverse experiences, orthostatic heart rate and blood pressure will be obtained after the patient has been supine for 5 minutes and then after the patient sits up with legs dependent for 1 minute.

At visits required within 24 hours of the occurrence of gastrointestinal adverse experiences (Section 8.1.2), a structured assessment of these adverse experiences including a physical examination will be performed as detailed in [Appendix F](#).

5.4.2 Electrocardiograph (ECG) (All Visits)

Greater than 2 hours after the patient's last short-acting beta2-agonist or greater than 12 hours after the last long-acting beta2-agonist administration, a 12-lead ECG will be performed at all visits including Follow-up (if abnormal at the previous visit) or upon early withdrawal after the patient has been semisupine for 5 minutes. Each ECG recording will be clearly labelled with patient initials, patient identification number, protocol number, centre number and date performed. The ECGs will be reviewed by the Investigator for clinically significant abnormalities. ECGs will be transferred to a centralised facility for data processing.

5.4.3 Laboratory Tests (All Visits)

Approximately 20 ml of blood will be collected for laboratory analyses at each visit and at early withdrawal. Blood and urine samples will be collected at the Follow-up Visit, only if abnormalities were observed at the previous visit. A urine pregnancy test will always be performed at the Follow-up Visit for women of child-bearing potential.

The following parameters will be measured:

Haematology: Haemoglobin concentration, haematocrit, red cell count, white cell count with differential, platelet count

Clinical chemistry: Blood urea, creatinine, aspartate transaminase (ASAT/SGOT), alanine transaminase (ALAT/SGPT), gamma glutamyl-transferase (GGT), alkaline phosphatase (ALP), total protein, albumin, total bilirubin, sodium, potassium, chloride, glucose, uric acid.

Amylase will be measured for patients who report gastrointestinal symptoms which are of concern to them or interfere with daily activities (see Section 8.1.2).

Faeces: Faecal occult blood tests will be performed at Weeks 24, 48 and annually thereafter, and at early withdrawal. Three tests collected on consecutive bowel movements, if possible, are to be performed according to the instructions provided with the faecal occult blood kits. In particular, patients are not to collect samples during or until 3 days after a menstrual period or while they have bleeding haemorrhoids or blood in the urine. In addition, patients are to avoid aspirin or other non-steroidal anti-inflammatory drugs for 7 days prior to and during the test period and to avoid Vitamin C in excess of 250 mg per day from all sources, red meat including processed meats and liver, and raw fruits and vegetables for 72 hours prior to and during the test period. When the samples are returned for analysis, the Investigator will question the patient to determine whether the instructions were followed.

Faecal occult blood will also be tested in patients who report gastrointestinal symptoms that are of concern to them or interfere with daily activities (see Section 8.1.2). When the samples are returned for analysis, the Investigator will question the patient to determine if the results may have been affected by menstruation, bleeding haemorrhoids, blood in the urine, medications, vitamins, or foods.

Urinalysis: Blood, glucose, protein, ketones.

Pregnancy: Serum beta-HCG for women of childbearing potential at 4-week intervals.

Urinary beta-HCG for women of child bearing potential at the Follow-up Visit.

Additional laboratory tests will be performed where indicated for patients who report gastrointestinal adverse experiences which are of concern to them or interfere with their daily activities (see Section 8.1.2).

The central laboratories, SmithKline Beecham Clinical Laboratories (SBCL) and Dorevitch Laboratories (Australia/New Zealand sites only) will be used for the routine haematological and biochemical assessments. All centres will send their samples to the SBCL or Dorevitch Laboratories. Samples must be clearly labelled with the patient number, patient initials, account number and requisition number. Full details for the preparation and shipment of samples will be provided by SBCL/Dorevitch to the Investigator before the start of the study. Urinalysis will initially be performed at the site using a dipstick provided by SBCL/Dorevitch. If abnormalities are found, full microscopy will be performed by SBCL/Dorevitch. Pregnancy testing at the Follow-up Visit will be performed locally using kits provided by SBCL/Dorevitch.

Reference ranges for all parameters will be obtained from the laboratory prior to starting the study and the tests should not be changed unless absolutely necessary during the study. If a change is unavoidable, the new reference range should be clearly identified in the CRFs concerned.

All clinically significant abnormal laboratory findings are to be repeated until the values return to normal. If such values do not return to normal within a period judged reasonable by the Investigator, the aetiology should be identified and the sponsor notified. Clinically significant worsening in laboratory findings must be recorded in the Adverse Experiences section of the CRF. Values outside of the reference range, but of no clinical significance, should be marked "NCS" by the Investigator on the printed laboratory report sheet.

5.4.4 Diary Card Completion

All visits (except Follow-up)

Diary cards will be issued at all on-therapy visits and will provide space for the patient to record if they feel differently since starting the study medication. This will help the patient to remember experiences that occur between visits that they want to discuss with the Investigator at the next visit.

5.4.5 Pulmonary Function Tests (All Visits Except at Week 1)

Preceding each clinic measurement of respiratory function, patients will have eaten breakfast but withheld the morning dose of study medication prior to the clinic visit, refrained from using inhaled short-acting beta₂-agonists or anticholinergic medications and not smoked for two hours before the visit. In addition, they will have refrained from using long-acting beta₂-agonists for

12-hours before the visit. At all visits, PFTs will be performed in the absence of beta₂-agonists and will be performed at trough (pre-dose) plasma levels of study medication.

Forced expiratory volume in one second (FEV₁), forced expiratory volume in 6 seconds (FEV₆), forced vital capacity (FVC), peak expiratory flow rate (PEFR), forced expiratory flow at 25-75% (FEF₂₅₋₇₅) of vital capacity and forced expiratory flow at 75% (FEF₇₅) of vital capacity will be measured according to the BTPS (Body Temperature and Pressure Standard) convention using the spirometer provided by SB which is suitable for research purposes, calibrated and maintained to acceptable respiratory function laboratory standards. The spirometry equipment provided by SB must be used for this study. All PFTs will be performed in accordance with the spirometry manual provided to each site. Pulmonary function tests will be performed after the patient has been at rest for at least 10 minutes after an exercise tolerance test. Pulmonary function tests will be repeated up to 8 times to obtain three acceptable readings according to ATS guidelines. [3] For each set of measurements, one FEV₁ must be within 10% of the highest value recorded.

5.4.6 Exercise Tolerance Test (12-week Intervals)

At 12-week intervals and early withdrawal, a 6-minute walk test as described by G. H. Guyatt and colleagues will be used to assess the functional capacity of the patient. [4]

The 6-minute walk will be conducted greater than 2 hours after the patient's last short-acting beta₂-agonist or greater than 12 hours after the last long-acting beta₂-agonist and where possible should be administered by the same person to avoid interrater variability. The patient will be instructed to walk from one end of a course to the other, covering as much ground as they can during 6 minutes. The patient will be encouraged to perform during the tests; the supervisor will face the patient every 30 seconds and deliver one of the following encouraging phrases:

"You're doing well!" or "Keep up the good work!"

At the end of the test, the supervisor will call out "Stop" and the distance walked by the patient will be measured and recorded on the CRF.

5.4.7 Breathlessness Assessment - Overall (All Visits Except Week 1) and Post-exercise (12-week Intervals, Early Withdrawal)

To assess overall breathlessness, patients will be asked the following question at all visits (except Week 1):

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

An assessment of breathlessness will also be made immediately following exercise testing at 12-week intervals (e.g., Weeks 12, 24, 36, 48) and at early withdrawal. Patients will be asked the following question:

[REDACTED]

For each assessment, patients will rate their breathlessness on a scale of 0 to 10, using the modified Borg scale (Table 2). [5] Investigators must show the scale to patients when the assessment is made. Responses are not limited to whole numbers.

Table 2 Breathlessness Assessment

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

6.0 Study Medication

6.1 Study Medication

SB 207499 will be provided as a film-coated, octagonal, yellow "Tiltab" tablet containing 15 mg of SB 207499.

6.2 Dosage and Administration

Patients will take one tablet in the morning after breakfast (ideally at 08:00) and one tablet after their evening meal (ideally at 20:00).

Tablets should be ingested with a glass of water. At each visit, patients will be instructed by the Investigator to attend the next visit not having taken the morning dose of study medication. These doses will be taken during the clinic visits (with food) at the instruction of the Investigator. **Note: The first dose of study medication for patients transferring from study 042 will not be taken at the first clinic visit of study 040. Instead, patients will take the first dose of study 040 medication in the evening allowing at least 8 hours since the last dose of study 042 medication taken in the clinic that morning.**

6.3 Method of Blinding

This is an open study.

6.4 Packaging

SB 207499 tablets will be provided in bottles containing either 70 or 210 tablets, corresponding to a 35-day or 105-day supply of study medication. Study medication will be issued at each clinic visit. For visits at 4-weekly intervals, one bottle of 70 tablets will be issued at each visit. For visits at 12-weekly intervals, either three bottles of 70 tablets, or one bottle of 210 tablets will be issued.

6.5 Labelling and Preparation

Patients will retain their patient identification number (PID) from study 042 or study 091. Study medication labels for all patients will not have pre-printed PIDs. Investigators must transcribe the patient initials, date dispensed and visit number for the patient onto the study medication labels.

A two-panel label consisting of a fixed portion and a tear-off portion will be attached to the medication bottles. The Investigator or his/her designate will remove the tear-off label from the bottle at the time of dispensing and attach it to the appropriate page in the CRF.

Labels will contain the following:

- Space to enter patient initials
- Space to enter date dispensed
- Space to enter visit number

Description of contents
Protocol number
Dosing directions
Storage conditions (room temperature)
Packaging (job) number
Batch number of tablets
Keep out of reach of children
Appropriate caution statements
Company address
Any other information specified by local regulatory requirements

6.6 Storage

Prior to dispensing, all study medication will be kept safely locked in a dry place at room temperature (at or below 30°C).

6.7 Drug Accountability

At the time of delivery of medication to the study site, the Investigator or designate will sign a Drug Receipt Form to confirm that the supplies for the study have been received. This form will specify supply or lot numbers, quantities shipped/delivered, and the date of receipt. The form will also contain statements confirming that

- The investigational products will be handled and stored safely and properly
- The investigational products will be dispensed only to patients in accordance with the protocol
- Any unused products will be returned to SmithKline Beecham.

The Investigator or designate will record all study medication dispensed on a Drug Accountability Form. At the conclusion of the study, reconciliation must be made between the amount of medication supplied, dispensed, and subsequently returned to SB. Any discrepancies must be accounted for. A certificate of return must be signed incorporating the assurance from the Investigator or designate that all used and unused investigational products have been returned. In the majority of cases, supplies will be returned to SB for subsequent destruction. In exceptional cases, supplies may be destroyed at the centre. Destruction should only be performed by authorised personnel who are aware of any possible hazardous effects, and following receipt of written approval from SB. The procedure should be documented in full, in writing.

6.8 Assessment of Compliance

Counts of tablets returned will be made at the beginning of all visits. Compliance (%) will be calculated according to the equation below and entered into the CRF:

$$\frac{\text{Number of tablets dispensed} - \text{number of tablets returned or lost}}{2 \times \text{number of days since last visit}} \times 100$$

Patients who show <80% or >120% compliance in taking study medication at two consecutive visits will not be permitted to continue in the study. Investigators will emphasise the importance of compliance in taking study medication to patients who are non-compliant after 1 week in the study (Visit 2).

6.9 Treatment of Study Medication Overdosage

Treatment of any suspected or confirmed overdose with SB 207499 should be symptomatic. Any instance of a suspected or confirmed overdose must be fully documented as a serious adverse experience and communicated to the SB Medical Monitor within 24 hours (Section 8.6).

6.10 Occupational Safety

Study medications are not expected to pose significant occupational safety risks to investigational staff under normal conditions of use and administration. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions is available upon request.

6.11 Concomitant Medication/Treatment

All concomitant medications taken during the study must be recorded in the CRF with the indication, unit dose and frequency, and dates of administration.

6.11.1 Inhaled Bronchodilators

The use of on-demand inhaled beta₂-agonists will be permitted throughout the study on an "as needed" basis, and will be recorded on the concomitant medication section of the CRF. Patients may continue to use whichever beta₂-agonists they use regularly. Investigators must note the name of the beta₂-agonists and strength per actuation in the CRF.

6.11.2 Anticholinergic Agents

The use of anticholinergic medication will be permitted during the study. Patients should continue to use their regular inhaler devices. Where possible, the dose of the medication should remain stable throughout open-label treatment. The use of inhaled anticholinergic medication must be recorded in the concomitant medication section of the CRF.

6.11.3 Other Concomitant Medications

There are no restrictions on the use of any concomitant COPD medication during the study with the exception of theophylline and aminophylline (oral or intravenous). Where possible, other COPD medication should be administered at stable doses. All concomitant medication taken during the study will be recorded in the CRF together with indication, daily dose, and dates of administration.

7.0 Outcomes Research and Pharmacoeconomics

7.1 Medical Care Utilisation Data Collection and Analysis

Medical care utilisation data will be collected in association with COPD disease exacerbations which require healthcare professional or medical intervention. Medical care utilisation includes hospitalisation, length of stay in intensive care units, emergency room visits, non-protocol physician office visits, physician office phone contacts for advice on management of an exacerbation, and medications used in the treatment of a COPD exacerbation (antibiotics, oral corticosteroids, beta₂-agonist via nebuliser or injection and oxygen). The medical care utilisation information will be collected in the CRF. Non-protocol medications used for the treatment of an exacerbation of COPD will be collected in the CRF.

7.2 Costs Associated With Lost Work Productivity

Data will be collected at each visit on the number of workdays lost as a result of an exacerbation episode. These data should be recorded in the CRF.

7.3 Quality of Life Analyses

Short-Form 36 (Appendix D)

The MOS Short-Form 36 is a generic quality of life assessment tool which has been used extensively to evaluate the physical, mental and general health status of patients. [6] The SF-36 will be administered at Week 0 and at 24-week intervals. Any patient who withdraws from the study should complete the SF-36 at the time of withdrawal (Section 5.3.8). The SF-36 will be scored using the standard scoring methodology described in the SF-36 reference manual. [7]

St. George's Respiratory Questionnaire (Appendix E)

It is clear that there is no universally accepted score for assessing symptoms in patients with COPD. The St. George's Respiratory Questionnaire (SGRQ) is a symptom-based, disease-specific quality of life instrument. [8,9,10] Advantages of using the SGRQ above other symptom-based assessments of disease status include the fact that it is validated in a number of different European languages and American English and a minimum clinically meaningful difference has been defined (4 unit change compared to placebo). [10]

The SGRQ is a self-administered questionnaire designed to measure and quantify the impact of chronic respiratory disease on health related quality of life and well-being. The SGRQ measures the impact of chronic respiratory disease on three domains: symptoms, activity and impact (on daily life). A total score is calculated for the entire questionnaire and for the 3 component domains. Guidelines for completion of the SGRQ are provided in Appendix E.

The SGRQ will be administered at Week 0, Week 12, Week 24 and at 24-week intervals thereafter. Any patient who withdraws from the study should complete the SGRQ at the time of the withdrawal (Section 5.3.8).

8.0 Adverse Experiences

The recording of adverse experiences is an important aspect of study documentation. Detailed guidelines are described in this section.

8.1 Eliciting and Documenting Adverse Experiences

It is the responsibility of the Investigator to document all adverse experiences which occur during the investigation.

An adverse experience includes any noxious, pathological or unintended change in anatomical, physiological or metabolic functions as indicated by physical signs,

symptoms and/or laboratory changes occurring in any phase of the clinical study, whether associated with the study drug or placebo, and whether or not considered drug related. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction or the significant worsening of the disease under investigation that is not recorded elsewhere in the CRF under specific efficacy assessments. Anticipated day-to-day fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening need not be considered adverse experiences. Discrete episodes of chronic conditions occurring during a study period should be reported as adverse experiences in order to assess changes in frequency or severity.

An adverse experience should be documented in terms of a medical diagnosis. When this is not possible, the adverse experience should be documented in terms of signs and/or symptoms observed by the Investigator or reported by the patient at each study visit.

Any pre-existing conditions or signs and/or symptoms present in a patient should have been recorded on the Medical/Surgical History form or as Adverse Experiences within the patient's CRF for study 042 and study 091.

All adverse experiences occurring after administration of the first dose of study medication (i.e., active drug) and on or before the final visit, must be reported on the Adverse Experience page in the patient's CRF, REGARDLESS OF WHETHER OR NOT THEY ARE CONSIDERED DRUG RELATED.

Serious adverse experiences which occur during the clinical study or within 30 days of receiving the last dose of study medication, whether or not related to study drug, must be reported.

Instances of death, cancer or congenital abnormality, if brought to the attention of the Investigator AT ANY TIME after cessation of study medication AND considered by the Investigator to be possibly related to study medication, should be reported to the SB Medical Monitor.

At each visit/assessment, adverse experiences will be evaluated by the Investigator. Adverse experiences not previously documented in the study will be recorded in the Adverse Experience Section of the patient's CRF. The nature of each experience, date and time (where appropriate) of onset, outcome, course (i.e., intermittent or constant), maximum intensity, action taken with respect to the investigational drug and relationship to treatment should be established. Details of changes to the dosage schedule or any corrective treatment should be recorded on the appropriate pages of the CRF.

Adverse experiences already documented in the CRF (i.e., at a previous assessment and designated as ongoing) should be reviewed at subsequent visits as necessary. If these have resolved, the documentation in the CRF should be completed. If an adverse experience changes in frequency or severity during a study period, a new record of the experience will be started.

As a consistent method of soliciting adverse experiences, ask the patient a non-leading question such as:

"Have you felt different in any way since starting the new treatment or since the last visit?"

In order to help the patient to remember and to answer this question accurately, the diary will provide space in which the patient may record if they felt different since starting the study medication.

8.1.1 COPD Exacerbation Definitions

An exacerbation of COPD is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.

Investigators will decide whether an exacerbation has occurred and the details will be recorded in a specific COPD exacerbation section of the CRF. COPD exacerbations are categorised as Level 1, 2, or 3, based on the treatment received by the patient for the exacerbation. The levels of exacerbations will be rated as follows:

Level 1 Exacerbation: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2 Exacerbation: Acute worsening of COPD that requires additional treatment (e.g., a short course of oral steroids, antibiotics, etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3 Exacerbation: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

If a patient has an exacerbation of COPD that is longer than 2 weeks in duration during the study, the Investigator will contact the SB Medical Monitor regarding the patient's continuation in the study.

Note: All exacerbations of COPD must be recorded in the COPD exacerbation section of the CRF. Any exacerbation of COPD, regardless of

level, that fulfils the SAE criteria must be recorded in the COPD SAE pages of the CRF.

8.1.2 Gastrointestinal Adverse Experiences

Adverse experiences related to the gastrointestinal tract will be closely monitored during this study. Patients will be instructed to call the Investigator to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The Investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of occurrence. This assessment will include a structured history of the adverse experience including relationship to the time of dosing with study medication and food intake; a physical examination with emphasis on the abdomen; and an assessment of orthostatic changes in heart rate and blood pressure. In addition, laboratory assessments will be performed: complete blood count with white cell differential; amylase, electrolytes, blood glucose, and liver function tests; urinalysis including microscopic examination, if indicated; and a faecal occult blood test. When the faecal occult blood test samples are returned for analysis, the Investigator will question the patient to determine if the results may have been affected by menstruation, bleeding haemorrhoids, blood in the urine, medications, vitamins, or foods. If a faecal occult blood test is positive or the patient has melaena, the patient will be referred to a gastroenterologist for a **complete** colonoscopy that emphasizes visualisation of the transverse colon with reporting of positive or negative findings, irrespective of other identified pathology or causes for gastrointestinal bleeding. Biopsies should be taken if appropriate. Results of the colonoscopy should be faxed to the Sponsor as soon as available.

Within 24 hours of notification by the patient, the Investigator will complete the GI AE Supplemental Form and fax it to the SB Medical Monitor.

The Investigator will review the results of the initial assessment and arrange further follow-up as appropriate. All events should be followed to resolution. If the patient experiences symptoms which are severe or persistent and considered by the Investigator to be study-drug related, withdrawal of the patient should be considered. Detailed guidelines for the assessment of gastrointestinal adverse experiences are presented in [Appendix F](#).

8.2 Assessment of Intensity

Maximum intensity of adverse experiences should be assigned to one of the following categories:

- Mild: An adverse experience which is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An adverse experience which is sufficiently discomforting to interfere with normal everyday activities.
- Severe: An adverse experience which prevents normal everyday activities.

8.3 Assessment of Causality

Every effort should be made by the Investigator to explain each adverse experience and assess its relationship, if any, to study drug treatment. Causality should be assessed using the following categories: not related, unlikely, suspected (*reasonable possibility*), and probable.

- Not related: The adverse experience is definitely not related to the study medication.
- Unlikely: There are other, more likely causes and the drug is not suspected as a cause.
- Suspected (*reasonable possibility*): A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but *there is a reasonable possibility that the experience was caused by the study medication*.
- Probable: There probably is a direct cause and effect relationship between the adverse experience and the study drug.

The degree of certainty with which an adverse experience is attributed to drug treatment or alternative causes (e.g., natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the experience can be understood in terms of one or more of the following:

- Known pharmacology of the drug
- Reaction of similar nature being previously observed with this drug or class of drug
- The experience having often been reported in literature for similar drugs as drug related (e.g., skin rashes, blood dyscrasia)
- The experience being related by time to drug ingestion terminating with drug withdrawal (dechallenge) or reproduced on rechallenge

8.4 Following-up of Adverse Experiences

Investigators should follow up patients with adverse experiences until the event has subsided (disappeared) or until the condition has stabilised. Reports relative to the patient's subsequent course of an adverse experience noted for any patient must be submitted to the SB Medical Monitor.

8.5 Serious Adverse Experiences

8.5.1 Definition of Serious Adverse Experiences:

A serious adverse experience is any event which is fatal, life threatening, disabling or incapacitating, or results in hospitalisation, prolongs a hospital stay or is associated with congenital abnormality, cancer or overdose (either accidental or intentional). In addition, any experience which the Investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug will be documented as a serious event.

Definition of "life threatening":

An adverse experience is life threatening if the patient was at immediate risk of death from the event as it occurred (i.e., it does not include a reaction that, if it had occurred in a more serious form, might have caused death). For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug induced hepatitis can be fatal.

Definition of "disabling/incapacitating":

An adverse experience is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the patient's ability to carry out normal life functions.

Definition of "hospitalisation":

Adverse experiences that require hospitalisation should be considered serious. Hospitalisation for elective surgery or routine clinical procedures that are not the result of an adverse experience (e.g., elective surgery for a pre-existing condition) need not be considered adverse experiences and should be recorded on the Medical/Surgical Procedures form in the CRF. If anything untoward is reported during the procedure, that occurrence must be reported as an adverse experience, either "serious" or "non-serious" according to the usual criteria.

In general, hospitalisation signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for

observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. When in doubt as to whether "hospitalisation" occurred or was necessary, the adverse experience should be considered serious.

Definition of "routine clinical procedure":

One which is defined in the protocol as a procedure which may take place during the study period and should not interfere with the study drug administration or any of the ongoing protocol specific procedures.

8.5.2 Reporting Serious Adverse Experiences

Any serious adverse experiences which occur at any time during the clinical study or within 30 days (or five half-lives, whichever is longer) of receiving the last dose of study medication, whether or not related to the study drug, must be reported by the Investigator to the local SB Medical Monitor by fax or telephone within 24 hours. If the GI AE of Concern also meets the criteria for a serious adverse event (SAE), the GI AE Supplemental Form, the Serious Adverse Experience CRF pages, CRF demography, medical history, prior/concomitant medications, study medication records, will also be faxed to GSK within 24 hours of notification by the patient.

Investigators should not wait to receive additional information to fully document the event before notifying SB of a serious adverse experience. The fax or telephone report should be followed by a full written summary utilising the SB Serious Adverse Experience form detailing relevant aspects of the adverse experience(s) in question. Where applicable, information from relevant hospital case records and autopsy reports should be obtained.

Instances of death, cancer or congenital abnormality, if brought to the attention of the Investigator AT ANY TIME after the cessation of study medication AND considered by the Investigator to be possibly related to study medication, should be reported to the SB Medical Monitor.

8.6 Reporting of Overdose

Any instance of overdose (suspected or confirmed, whether or not it involves the study medication) must be communicated to SB within 24 hours and be fully documented as a serious adverse experience. Details of any signs or symptoms and their management should be recorded including details of any antidote(s) administered (Section 6.10).

8.7 Pregnancy

Patients who become pregnant during the study should be withdrawn from the study immediately.

Patients should be instructed to notify the Investigator if it is determined after completion of the study that they became pregnant either during the treatment phase of the study or within 30 days after the treatment period.

Whenever possible, a pregnancy should be followed to term, any premature terminations reported and the status of the mother and child after delivery should be reported to SB.

9.0 Patient Completion and Withdrawal

9.1 Definitions

Premature termination is defined as withdrawal of the patient for any reason before the last on-therapy visit at Week 96.

9.2 Procedures for Handling Withdrawals

Patients who terminate their participation in the study because of adverse experiences should be followed up as appropriate (Section 8.4) in order to determine the final outcome of the adverse experience.

All patients who withdraw or are withdrawn from the study should complete the assessments and procedures scheduled for early withdrawal (Section 5.3.8), wherever possible.

The CRFs of *all* patients entered into the study must be kept, and the reasons for withdrawal will be noted on the study conclusion page for all enrolled patients who do not complete the study. In addition, the date of the last dose of study medication must be recorded on the study conclusion page for all patients withdrawn from the study.

9.3 Reasons for Withdrawal

Every effort must be made by the Investigator to keep patients in the study. However, a patient may be discontinued prior to completion of the study for the following reasons:

- **Adverse experience** (Section 8.0): This includes a deterioration in COPD or COPD exacerbation resulting in a patient being withdrawn.
- **Lack of efficacy**: This includes a desire by the patient/Investigator that the patient be withdrawn from the study because of no improvement in COPD symptoms. It **does not** include a deterioration in COPD or COPD exacerbation which must be regarded as an adverse experience.
- **Conduct of Study Deviation**: This includes lack of compliance (dosing, visit schedule).
- **Patient lost to follow-up**
- **Termination** of the study by SmithKline Beecham
- **Other** (reason to be documented in the CRF).

All adverse experiences leading to withdrawal of a patient must be fully documented and followed-up as appropriate (Section 8.0). To ensure that all withdrawals due to adverse experiences are correctly identified, "Adverse Experience" should only be checked as the reason for withdrawal on the Study Conclusion page for those patients for whom an adverse experience was considered to be the direct cause of the patient withdrawing from the study. This is particularly important when adverse experiences are ongoing at the time of withdrawal but the reason for withdrawal is not related to the adverse experiences.

10.0 Data Evaluation

The Biometrics Unit of SmithKline Beecham Pharmaceuticals will perform all statistical analyses.

10.1 Target Sample Size

No formal power calculations were performed since this is an open-label study with the primary purpose of evaluating patient safety. It is estimated that approximately 600 patients will be enrolled at 200 centres in Europe, South Africa and Australia/New Zealand participating in study 042 or study 091.

10.2 Method of Randomisation

This is an open-label study. All patients will receive SB 207499 15 mg bid.

10.3 Planned Efficacy Analysis

10.3.1 Efficacy Variables

- Clinic trough FEV₁, FEV₆, FVC, FEF₂₅₋₇₅, FEF₇₅, and PEFr
- Overall and post-exercise breathlessness (Borg scale)
- Total and subscale scores of the SGRQ
- Exercise performance (distance walked during 6-minute walk)
- SF-36 (generic quality of life)
- COPD exacerbation rates
- Health economic measures (days off work, healthcare utilisation)

10.3.2 Derivation of Efficacy Variables for Analysis

For each clinic pulmonary function parameter, three adequate readings will be collected at each scheduled evaluation. The highest of the three readings will be used in the analysis. If more than one set of readings is available for a particular assessment, the later of the two readings will be used in the analysis. For the SGRQ and SF-36 scores will be derived according to algorithms provided by the scales developers. Change from baseline will be calculated for all continuous efficacy parameters as the difference between the visit evaluation and the baseline evaluation. Baseline is defined as the predose evaluation at Visit 3 of the parent study.

10.3.3 Populations to be Evaluated

All efficacy analyses will be based on the population of patients who receive at least one dose of study medication and have at least one efficacy evaluation during the study. Description of efficacy variables will be by randomised treatment group in the parent study.

If there is adequate sample size additional analyses will be performed based on use of concomitant COPD medication use.

10.3.4 Comparisons of Interest

The primary comparison of interest will be the within group change from the baseline assessment of the parent study (study 042 and study 091).

An additional comparison will be a within group change from Visit 1 of study 040 for patients randomised to placebo in the parent study.

No comparison between the two groups will be performed.

10.3.5 Methods of Analysis

Descriptive statistics will be provided for all demographic and baseline characteristics.

For continuous efficacy endpoints defined in Section 10.3.1, descriptive statistics (including mean, median, range, standard deviation and 95% confidence intervals) will be provided for the change from baseline at each scheduled study visit. No statistical hypothesis testing will be performed.

Annualised rates for COPD exacerbations and resource utilisation will be estimated using a Poisson regression model.

10.4 Planned Safety Evaluation

Evaluation of safety data will include all patients who receive at least one dose of study medication. Primary consideration will be given to presentation of the safety data without regard to randomised treatment in the feeder study. A secondary presentation of safety data will by randomised treatment in the feeder study

Adverse experiences will be summarised by time to onset, severity, and Investigator-reported relationship of the adverse experience to study medication. Gastrointestinal adverse experiences of concern will be summarised separately. The proportion of patients withdrawn due to adverse experiences and due to gastrointestinal adverse experiences of concern will be evaluated.

For clinical laboratories, vital signs and ECG intervals descriptive statistics will be provided at each visit. For clinical laboratories the percentage of patients outside the normal limits and with values of sponsor-defined clinical concern will be tabulated across all on-therapy visits. Vital signs of clinical concern, orthostatic vital signs of clinical concern and ECGs of clinical concern will be tabulated in similar manner. Orthostatic vital signs of clinical concern will be summarised for all patients enrolled and the subgroup of patients with gastrointestinal adverse experiences of concern. Clinical concern criteria will be documented separately. In addition ECG abnormalities will be summarised using SNOMED terminology.

The proportion of patients with positive faecal occult bloods on-therapy will be tabulated for all enrolled patients and the subgroup of patients with gastrointestinal adverse experiences of concern.

Exploratory analyses will be performed to further characterise gastrointestinal adverse experiences of concern.

10.5 Interim Analysis

This is an open-label study. Data will be evaluated on an ongoing basis.

11.0 Administrative Matters

To comply with Good Clinical Practice, important administrative obligations relating to Investigator responsibilities, monitoring, archiving data, audits, confidentiality and publications must be fulfilled as given in [Appendix B](#).

12.0 References

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13.0 Appendices

Appendix A: World Medical Association Declaration of Helsinki

Recommendations guiding physicians in
biomedical research involving human subjects

Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964
Amended by the 29th World Medical Assembly,
Tokyo, Japan, October 1975
35th World Medical Assembly,
Venice, Italy, October 1983
and the
41st World Medical Assembly
Hong Kong, September 1989
and the
48th General Assembly
Somerset West, Republic of South Africa, October 1996.

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration", and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice, most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognised between medical research in which the aim is essentially diagnostic or therapeutic

for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings for further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

- 1 Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
- 2 The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the Investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
- 3 Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
- 4 Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
- 5 Every biomedical research project involving human subjects should be preceded with careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

- 6 The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
- 7 Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
- 8 In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
- 9 In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.
- 10 When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case, the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.
- 11 In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
- 12 The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical Research)

- 1 In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.
- 2 The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
- 3 In any medical study, every patient including those of a control group, if any, should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
- 4 The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
- 5 If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I,2).
- 6 The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-Clinical Biomedical Research)

- 1 In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
- 2 The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.
- 3 The Investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.
- 4 In research on man, the interest of science and society should never take precedence over considerations related to the well being of the subject.

Appendix B: Administrative Matters

I. RESPONSIBILITIES OF THE INVESTIGATOR

- To ensure that he/she has sufficient time to conduct and complete the study, and has adequate staff and appropriate facilities which are available for the duration of the study, and to ensure that other studies do not divert essential subjects/patients or facilities away from the study at hand.
- To submit an up-to-date curriculum vitae and other credentials to the sponsor and - where required - to relevant authorities.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the Laboratory License or Certification.
- To prepare and maintain adequate case histories designed to record observations and other data pertinent to the study.

II. PROTOCOL AMENDMENTS

No changes to the study protocol will be allowed unless discussed in detail with the SmithKline Beecham (SB) Medical Monitor and filed as an amendment/modification to this protocol.

Any amendment/modification to the protocol will be adhered to by the participating centre (or all participating centres) and will apply to all subjects following approval as appropriate by the Ethical Review Committee or Institutional Review Board.

III. SPONSOR'S TERMINATION OF STUDY

SB reserves the right to discontinue the clinical study at any time for medical or administrative reasons. When feasible, a 30-day written notification will be tendered.

IV. CASE REPORT FORM INSTRUCTIONS

Prior to screening the first potential participant, the Investigator will provide a list showing the signature and hand-written initials of all individuals authorised to

make or change entries on CRFs. If the authorised individuals should change during the study, the Investigator is to inform SB.

CRFs will be supplied by SB for recording all data. It is the responsibility of the Investigator to ensure that CRFs are legible and completely filled in with a black ink ball-point pen. The subject's identification (2-3 alphabetic letters representing the subject's initials or first letter of subject's name), the patient identification (PID) if not already pre-printed and the visit date will be entered on the CRF Header Pages as required.

Errors must be corrected by drawing a single line through the incorrect entry and writing in the new value/data positioned as close to the original as possible. The correction must then be initialled, dated and justified by the authorised individual making the change. Do not obliterate, write over or erase the original entry when making a correction.

When a subject completes a visit, it is anticipated that relevant sections of the CRF will be completed by the Investigator (or designated staff member) within 24 hours of the last data becoming available, but in no case later than five days. Similarly, when a subject completes a study, it is anticipated that all relevant CRF pages will be completed within 24 hours of the last data becoming available, but in no case later than five days. This also applies to forms for potential study participants who were not randomised to a treatment group.

As soon as the subject has completed/withdrawn from the study and the CRF is completed, the principal Investigator or designated physician(s) under his/her supervision will sign the adverse experience page(s) as well as study conclusion page of the CRF to confirm that they have reviewed the data and that the data are complete and accurate. If sections of a CRF are to be brought into SB prior to study conclusion, a Section conclusion signature is required.

An original (top copy) CRF must be submitted for all subjects who have undergone protocol specific procedures, whether or not the subject completed the study.

While completed CRFs will be reviewed by an SB professional monitor at the study sites, errors detected by subsequent in-house CRF review may necessitate clarification or correction of errors and documentation and approval by the Investigator.

Any questions or comments related to the CRF should be directed to the assigned SB Medical Monitor.

V. MONITORING BY SMITHKLINE BEECHAM

Monitoring visits by a professional representative of SB (the sponsor) will be scheduled to take place before study initiation and at appropriate intervals during the trial and after the last subject has completed the study.

These visits are for the purpose of verifying adherence to the protocol and the completeness and exactness of data entered on the CRF and Drug Inventory Forms. The monitor will verify CRF entries by comparing them with the hospital/clinic/office records which will be made available for this purpose. The monitor will retrieve completed CRF sections at each visit. Adequate time and space for these visits must be made available by the Investigator.

The Investigator must ensure provision of reasonable space and adequate qualified personnel for monitoring visits.

VI. ARCHIVING OF DATA

The Investigator must retain subject records, CRFs and drug disposition records in an easily retrievable form for 15 years after completion or until disposal has been agreed in writing with SB, whichever is sooner. The Investigator must have a 'key' linking the subject's study identification number (i.e., treatment number) to the subject's clinical file. If the Investigator moves or retires, he/she must nominate someone in writing to be responsible for record keeping. Archived data may be held on microfiche or electronic record, provided that a back-up exists and a hard copy can be obtained from it, if required.

SB agrees to retain a copy of the protocol, documentation, approvals and all other documents related to the study, including certificates that satisfactory audit and inspection procedures have been carried out. SB also agrees to provide copies to the Investigator should he/she wish another copy.

VII. AUDITS

For the purpose of compliance with Good Clinical Practice and Regulatory Agency Guidelines, it may be necessary for SB or a Drug Regulatory Agency to conduct a site audit. This may occur at any time from start to after conclusion of the study.

When an Investigator signs the protocol, he agrees to allow the Drug Regulatory Agency and SB auditors to inspect his/her study records. Furthermore, if an Investigator refuses an inspection, his data will not be accepted in support of a New Drug Registration and/or Application.

SB has a substantial investment in clinical studies. Having the highest quality data and studies are essential aspects of drug development. SB has a Regulatory Compliance staff who audits investigational sites. Regulatory Compliance assesses the quality of data with regard to accuracy, adequacy and consistency. In addition, Regulatory Compliance assures that SB-sponsored studies are conducted in accordance with Good Clinical Practices standards and that relevant regulations/guidelines are being followed.

To accomplish these functions, Regulatory Compliance selects investigational sites to audit. These audits usually take one to two days. The SB audits entail review of source documents supporting the adequacy and accuracy of CRFs, review of documentation required to be maintained and checks on drug accountability. The SB audit therefore helps prepare an Investigator for a possible regulatory agency inspection, as well as assuring SB of the validity of the database across investigational sites.

The Inspector will be especially interested in the following items:

- Log of visits from the sponsor's representatives
- IRB/ERC approval
- Study medication accountability
- Approved study protocol and amendments
- Signed informed consent of the subjects
- Medical records including laboratory data to support entries in the CRF
- Correspondence between the IRB/ERC and the sponsor
- Record retention

SB will gladly assist investigators prepare for a regulatory agency inspection.

VIII. CONFIDENTIALITY AND PUBLICATION

The Investigator agrees that all information provided by SB is the exclusive property of SB and that the same shall be kept strictly confidential by the Investigator or any other person connected with the work and shall not be disclosed by the Investigator or such person to any third party without the prior written consent of SB. The Investigator shall communicate the results of the work promptly to SB.

SB agrees that the Investigator shall have the right to publish or permit the publication of any information or material relating to or arising out of the work after prior submission to SB provided that, if SB shall so requests, the Investigator will delay publication for a maximum of six months to enable SB to protect its rights in such information or material. Any proposed publication or presentation (e.g., manuscript, abstract or poster) for submission to a journal or scientific meeting should be sent to the SB Medical Monitor prior to submission. SB will undertake to comment on such documents within four weeks.

All rights and interests world-wide in any inventions, know-how or other intellectual or industrial property rights which arise during the course of and/or as a result of the clinical study which is the subject of this Protocol or which otherwise arise from the information or materials supplied under this Agreement, shall be assigned to, vest in and remain the property of SmithKline Beecham plc.

Appendix C: Sample Informed Consent

WRITTEN INFORMED CONSENT TO PARTICIPATE IN A CLINICAL STUDY OF AN INVESTIGATIONAL DRUG

INVESTIGATOR: (Name, Address, Phone)

STUDY TITLE: A multicentre, open-label extension study to evaluate the safety, tolerability and efficacy of oral SB 207499 (15 mg twice daily) in patients with chronic obstructive pulmonary disease (COPD).

PROTOCOL NO.: 207499/040

SPONSOR: SmithKline Beecham Pharmaceuticals ("The Company")

Dear Patient

We would like you to consider taking part in this medical research study assessing the long-term safety and effectiveness of a new treatment - "SB 207499" because you suffer from chronic obstructive pulmonary disease (COPD). This is an extension study to the previous study (study 042 or study 091) which you have completed.

However, before you decide whether or not to take part, please read the following information carefully and ask any questions you have. Before taking part in the study, it is necessary for you to give your written consent to participate.

Nature and Purpose of the Study

SB 207499 is a new type of drug called a "phosphodiesterase inhibitor".

Phosphodiesterases, which are substances in the body, may be involved in producing some of the symptoms of COPD. If the effects of phosphodiesterases in the lungs can be blocked by SB 207499, the course of COPD may be improved.

To date, SB 207499 has been given to 1068 patients with COPD and asthma in research studies. These studies have shown that the new medication appears to be safe and data from a study in patients with COPD showed that the dose to be used in this study was of benefit by reducing symptoms and improving lung function. The most common side effects known at this time are headache, nausea,

diarrhoea, abdominal pain, indigestion and vomiting, the majority of which have been mild or moderate and have not required treatment. Due to these side effects being mostly gastrointestinal (in the stomach area) you will be asked to make a note of these symptoms in a diary card during the study to better describe the nature of these symptoms. In addition, if you experience gastrointestinal symptoms that are of concern to you or interfere with your daily activities you should contact your study doctor as soon as possible so she/he can decide whether other tests are appropriate.

In this study you are given two tablets of medication per day (each containing 15 mg of SB 207499). One tablet should be taken immediately after your breakfast and the other tablet taken immediately after your evening meal each day.

What Does the Study Involve

This extension study is planned to last for a period of 96 weeks of treatment. It is anticipated that approximately 600 patients will take part in this study. Before starting the study, you will have given your written consent to take part.

If you qualify for the study, you will be given the study medication. You will also be asked to complete a diary card to write down if you feel differently since starting study medication and to record the date of onset.

You will be asked to visit the clinic weekly for two weeks, then once a fortnight and then every month. You should make sure that you have eaten breakfast and that you do not take your morning dose of study medication before each visit. Also, you will be asked not to use your inhaler(s) or smoke for 2 hours before the visits or during the clinic visit.

The following tests will be carried out:

- Lung function tests (spirometry) will be measured at every visit (except the 2nd Visit).
- A physical examination will be performed at visits 1, 9 and 15 and then every 24 weeks.
- Blood pressure and heart rate will be measured at every visit.
- At each visit you will have small wires stuck to your body at several places to record an (ECG). This will measure the electrical activity of your heart.
- An exercise test, involving 6 minutes of walking, will be carried out at visits 1, 6, 9, 12 and 15 and then every 12 weeks to look at how well your lungs work during exercise. After walking, your heart rate and the amount of

oxygen in your bloodstream will be measured through your skin with a device clipped on your finger or ear.

- Blood (20mls) and urine(10mls) samples for routine laboratory tests will be taken at every visit. Pre-menopausal women will be asked to produce one urine sample for pregnancy testing at the Follow-up visit.
- You will be given questionnaires to complete at visits 1, 6, 9 and 15 and then every 24 weeks to assess your quality of life.
- Three pea-sized faecal samples will be requested for collection at 24 weeks, 48 weeks and annually thereafter and if you withdraw early from the study to test for bleeding in your gastrointestinal system. Three tests collected on consecutive bowel movements, if possible, are to be performed according to the instructions provided with the faecal occult blood kits. In particular, you will be asked not to collect samples during or until 3 days after a menstrual period or while you have bleeding haemorrhoids or blood in the urine. You will be asked to avoid taking aspirin or other non-steroidal anti-inflammatory drugs (such as ibuprofen or naproxen) for 7 days before and during the test period. For 72 hours before and during the test period, you will be asked NOT to take more than 250 mg of Vitamin C per day and NOT to eat red meat (including processed meats and liver) or raw fruits and vegetables (especially melons, radishes, turnips, and horseradish). When the samples are returned for analysis, the Investigator will ask if you followed the instructions.

After the last visit, you will be asked to return to the clinic for a safety follow-up visit where a physical examination, ECG and blood sample may be requested by your doctor.

Certain medications are not allowed during the study. Your doctor will give you a list of these prohibited medications. Also please check with your doctor before taking any 'over-the-counter' medications.

Pregnancy

The effects of SB 207499 on an unborn baby are uncertain and so you will not be allowed to participate in this study if you are pregnant. If there is any chance you could become pregnant during the study, you must use one of the allowed contraceptive methods. Also, if appropriate, you will be tested during the study to determine whether you might have become pregnant. If you do become pregnant you must stop taking the study medication immediately and contact your doctor. You should also tell your doctor if you become pregnant within a month of completing the study.

What are the Risks Associated with the Study

All drugs may cause side-effects in some patients. At the dose used in this study, the most common side-effect of SB 207499 known at this time are headache, nausea, diarrhoea, abdominal pain and indigestion. Vomiting and dizziness have also been observed in some volunteers, but generally at higher doses than that being studied here and these side-effects resolved with no treatment. In the interest of your safety, SB is researching these gastrointestinal complaints. If you experience black or bloody stools, abdominal discomfort, such as pain or cramps, diarrhea, or vomiting that cause you concern or interfere with daily activities (including eating or sleeping), you will be asked to contact your Investigator and you will visit the clinic within 24 hours. At the clinic, your doctor will discuss the complaint with you, complete a physical examination of the abdomen, and measure your blood pressure in the lying and sitting positions. Blood will be drawn and you will give a sample of urine. Your doctor will also give you a faecal occult blood test kit to test for gastrointestinal bleeding. You will use this kit to obtain small stool samples at home to be returned to the clinic for analysis. The doctor will ask if you have been menstruating, had bleeding haemorrhoids, or had blood in the urine, and will also question you about the medications, vitamins, and foods you have been taking. If the faecal occult blood test indicates that you have blood in your stool, you will be referred to a gastroenterologist for a colonoscopy. You will also be referred for a colonoscopy if you have black, tarry, or bloody stools or if you pass blood from the rectum. Additional tests or procedures might be performed at the discretion of your doctor. Your progress will be followed daily thereafter until you feel better and you and your doctor decide that the problem is resolved.

Certain procedures, including some lung function tests, heart rate and blood pressure monitoring, form part of the study. These investigations would normally be carried out by a doctor in routine examination of your condition. However, during this study ECG recordings will also be made and blood samples will be taken. You may experience some discomfort and bruising at the injection site where you have blood taken from. The drugs used in this study may involve other risks that are not known at this time.

What are the Benefits

You and other patients with COPD in the future may benefit from any experimental research. Such benefits include the possibility that your condition may improve and that this study may help develop a new therapy for others with similar conditions.

New Information

If we receive any new information about the study drug and its side-effects we will inform you.

Alternative Treatments

There are alternative therapies for COPD. Your doctor will discuss the availability and effectiveness of alternative therapies.

Confidentiality

The information collected about you during the study is strictly confidential. For purposes of the study, your medical notes may be made available to the sponsoring company (or representatives) or medical regulatory bodies for the purposes of medical research or for effecting registration of the drug or as may be required in law. If you decide to take part in the study your General Practitioner (GP) will be informed.

Compensation/Costs

If you become ill or injured as a result of participation in this study, medical treatment will be provided, and reasonable costs of such treatment will be met by the sponsoring company. If you have any questions concerning the availability of medical care or if you think you have experienced a research-related injury, contact:

Name: _____ Tel: _____

The sponsoring company will reimburse you for any reasonable additional costs incurred as a participant in this study, i.e. travel expenses to and from the clinic upon presentation of receipts.

What if I Choose Not to Take Part or Want to Stop During the Study

Participation is entirely voluntary. If you decide not to take part you do not need to give any reasons and your medical care will not be affected in any way. You are free to withdraw from the study at any time and do not need to give a reason for doing so.

If you should withdraw from the study, or the doctor has decided it is in your best interest to leave the study, you will be asked about your experience with the study drug and will be asked to have a final medical check. If you withdraw between scheduled visits you will be asked to contact your study doctor to arrange an appointment as soon as possible. You will also be asked to co-operate in having

a laboratory test, a physical examination and to return in 7 days time for a final safety visit.

Questions

You are encouraged to ask questions at any time during the study. If you have a problem or have more questions about the study, please call your doctor as follows:

Contact Name _____

Telephone _____

In case of emergency outside of normal hours or a Gastrointestinal upset:

Contact Name _____

Telephone _____

CONSENT STATEMENT

Study Title: A multicentre, open-label extension study to evaluate the safety, tolerability and efficacy of SB 207499 (15 mg twice daily) in patients with chronic obstructive pulmonary disease (COPD)

Patient Initials _____

Patient Study Number _____

Patient:

I have read the information document and have been given a copy to keep. The study has been explained to me and I have had a chance to ask any questions and all my questions have been answered. I understand that I am free to withdraw from this study at any time without it affecting my medical care. I give consent to the sponsoring company or their representatives to inspect my medical documents for the purposes of the research. By signing this form I give my free and informed consent to take part in this study.

Patient's Signature _____

Patient's Name _____

Date _____

Investigator:

I have fully explained the details of this study to the above named patient. I have explained to the patient his/her freedom to withdraw from the study at any time. I have answered all the questions the patient has at this time and I have offered to answer any future questions. I have informed the patient of whom to contact in the event of a research-related injury. I have provided written information to be taken away by the patient for future reference.

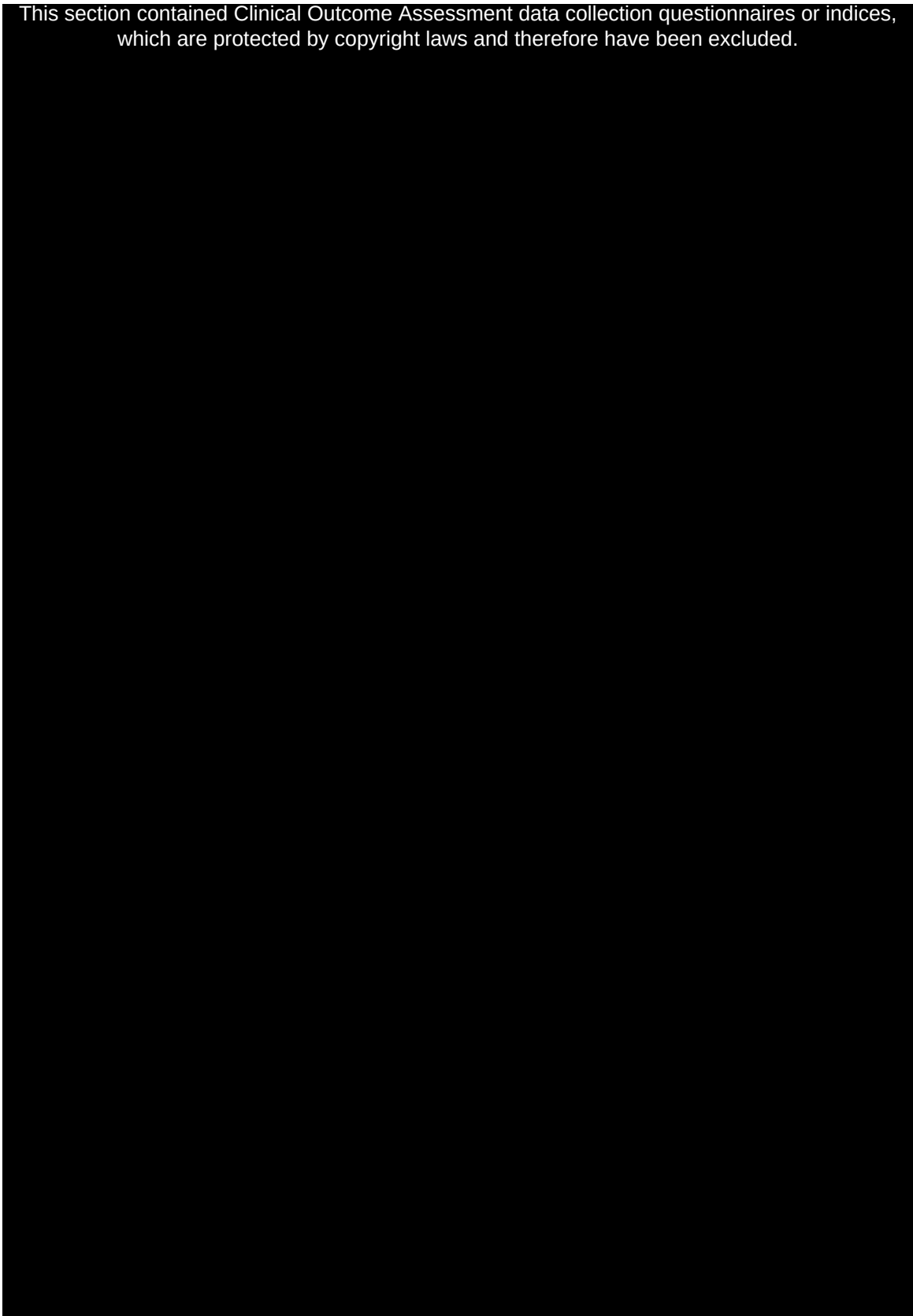
Investigator's Signature _____

Investigator's Name _____

Date _____

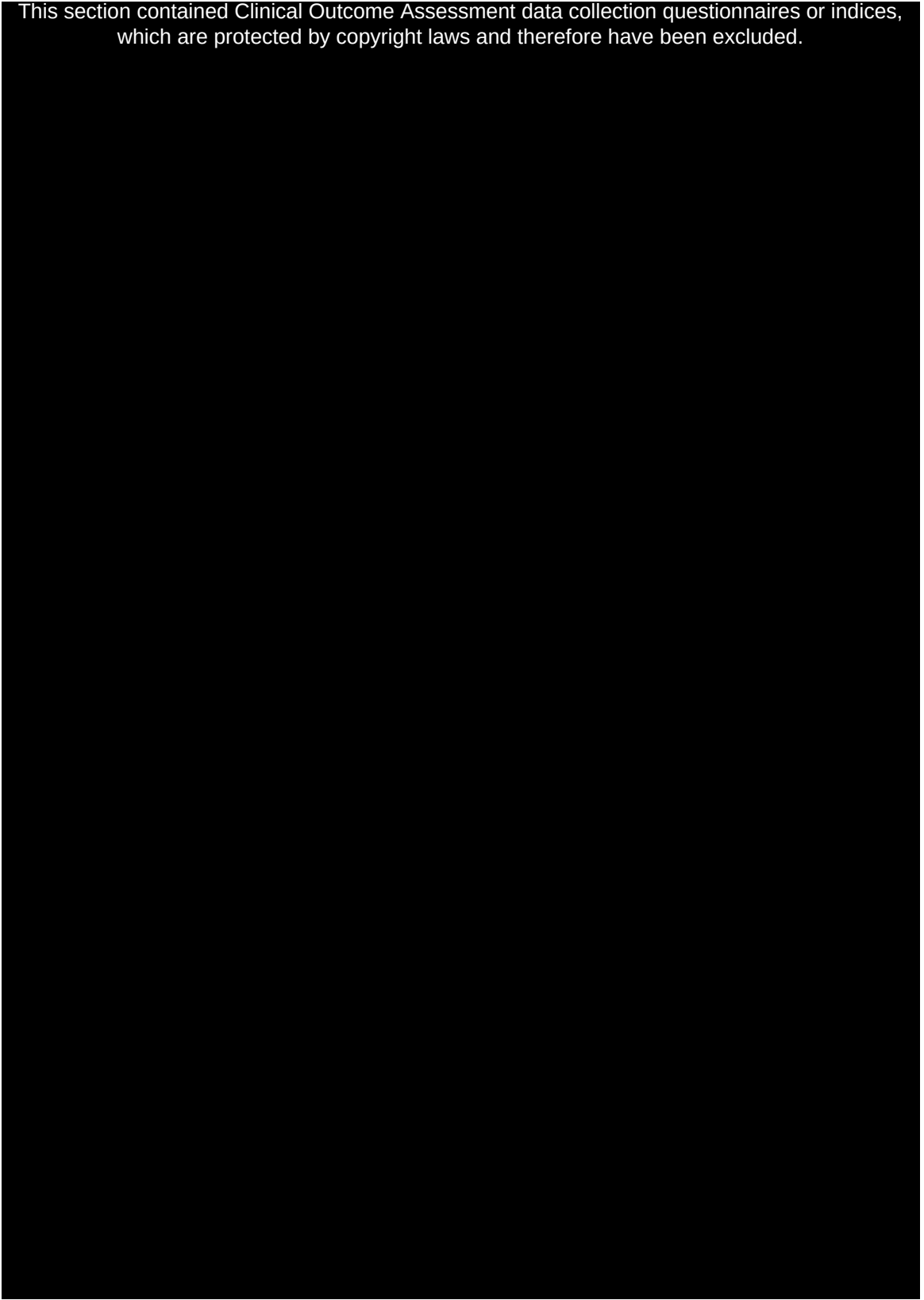
Appendix D: The SF-36 Health Survey Questionnaire

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.



Appendix E: The St George's Respiratory Questionnaire

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.



Appendix F: Gastrointestinal Adverse Experience Monitoring

1. Introduction

Adverse experiences related to the gastrointestinal tract will be closely monitored during this study and gastro-intestinal related symptoms should be recorded on the patient's diary card.

Patients will be instructed to call the Investigator to report any gastrointestinal symptoms which cause them concern or interfere with their daily activities, in particular those which may be associated with acute or chronic gastro-intestinal blood loss such as bloody or black stools, abdominal discomfort pain or cramps and diarrhoea or vomiting. The Investigator must complete a clinical assessment of these gastrointestinal adverse experience(s) within 24 hours of the patient reporting them; he/she should then fax the completed G.I. adverse experience forms to the SB monitor within 24 hours of the clinical assessment.

In order to provide consistent data relating to all of these gastrointestinal adverse experiences, a specific format will be followed for history, physical examination and laboratory assessment of these patients. The format is outlined below and supplied in the CRF. Referral to a gastroenterologist is mandatory if the patient has a positive faecal occult blood test or melaena. (See [2.2 Additional Testing](#)).

2. Assessments of Gastrointestinal Adverse Experiences

2.1 Initial assessment

This assessment will be performed on all patients who report gastrointestinal symptoms which may be associated with acute or chronic gastro-intestinal blood loss such as bloody or black stools, abdominal discomfort pain or cramps and diarrhoea or vomiting. The assessment must include, a history, physical examination and laboratory assessment. Patients who have a positive faecal occult blood test or melaena must be referred to a gastroenterologist for a colonoscopy. The following information will be documented in the CRF.

History:

The investigator will elicit the history of the symptom with attention to the following features:

Pain; Spatial characteristics; Quality of the pain; Temporal nature of the pain; Does the pain radiate?; Time of onset of gastrointestinal symptom; Time of last dose of study medication.

Physical Examination

- Assessment of general appearance to assess for signs such as jaundice
- Abdominal examination to assess bowel sounds, abdominal tenderness, abdominal masses, and peritoneal signs
- Heart rate and blood pressure, performed while patient is supine followed by sitting with legs dependent, to assess orthostatic changes.

Other significant findings.

Laboratory assessments:

- Faecal occult blood (using a patient collection kit and an investigator analysing kit)
- Urinalysis
- Complete blood count with differential
- Amylase
- Electrolytes
- Blood glucose
- Liver function tests

2.2 Additional Testing

Referral to a gastroenterologist is mandatory if the patient has a positive faecal occult blood test or melaena. The colonoscopy must be **complete** with emphasis on visualisation of the transverse colon and reporting of positive or negative findings, irrespective of other identified pathology or causes for GI bleeding. Biopsies should be taken if appropriate. Results should be faxed to the Sponsor as soon as available.

Additional tests and procedures that may be necessary to diagnose the gastrointestinal adverse experience and/or treat the patient will be performed at the discretion of the Investigator, including, but not limited to, the following:

- Flat plate, upright, decubitus X-ray of abdomen
- Rectal/pelvic examination
- Ultrasound of abdomen
- CT of abdomen
- Stool for ova and parasites
- Other diagnostic tests as deemed necessary by the investigator
- Referral to gastroenterologist, surgeon, or other specialist
- Consider withdrawal for patients with severe or persistent symptoms that may be drug related.

If additional tests are performed, reports should be faxed to the Sponsor as soon as available.

F2.2 Daily Follow-up Assessments

Patients who report gastrointestinal adverse experiences which cause them concern or interfere with usual activity will be assessed daily until the adverse experience resolves. Patients can return to the clinic for these evaluations or the Investigator may designate a qualified health care provider to perform the follow-up assessments. These assessments will include an interim history, interim physical examination, and interim laboratory assessment.

Reporting And Analysis Plan

April 12, 1999

Revised (October 21, 1999)

Revised (January 21, 1999)

Revised (August 7, 2000)

Final

A multicentre, open-label extension study to evaluate the safety, tolerability and efficacy of oral SB 207499(15 mg twice daily) in patients with chronic obstructive pulmonary disease (COPD).

SB-207499

(A Phosphodiesterase IV Inhibitor)

Protocol

SB-207499/040

██████████ MSc.** ██████████ MS*
██████████ BSc.** ██████████ BS*

*Biometrics, SmithKline Beecham, USA **Cardiopulmonary Therapeutic Unit, SmithKline Beecham, USA

I. STUDY OBJECTIVES

To evaluate the long-term safety and tolerability of SB 207499 (15 mg bid) in patients with COPD.

To further evaluate clinical efficacy of SB 207499 in terms of pulmonary function, disease symptoms and quality of life.

II. STUDY DESIGN

This study is an open-label extension study, designed to assess the long-term safety, tolerability and efficacy of SB 207499 15 mg twice daily. This study is open to patients who complete study 042 or study 091 including all assessments at the last double-blind visit.

The study will continue until registration of the product or termination of the program by the sponsor.

III. STUDY METHODOLOGY

Patients will be assessed for their eligibility for study 040 at their final scheduled visit (prior to Safety Follow-up visit) in study 042 or study 091. Eligible patients will receive SB 207499 at a dose of 15 mg bid for the duration of the study. The study blind from the previous study will not be broken before entering patients into study 040. With the exception of theophylline or aminophylline (oral or intravenous) other COPD medication is permitted to be used concomitantly with SB 207499.

For each scheduled study visit, patients will be required to attend the clinic in the morning, at about the same time of day (preferably 10:00 ± 2 hours), not having taken the morning dose of study medication, and having refrained from using beta₂-agonists (short-acting), anticholinergic medications and smoking during the two-hour period and from using beta₂-agonists (long-acting) during the 12-hour period preceding the visit.

Smoking and the use of beta₂-agonists or anticholinergic treatment must be avoided during the clinic stay if at all possible. Patients must **not** take their morning doses of study medication before attending morning clinic visits.

Following Week 4, visits will be scheduled every four weeks. Pulmonary function and overall breathlessness (Borg Scale) will be evaluated at each visit. The six-minute walk and related assessments will be evaluated every 12 weeks. Health-related quality of life assessment (SF-36 and SGRQ) will be assessed at 12 and 24 weeks and every 24 weeks thereafter.

IV STUDY POPULATION AND DEFINITION OF SUB-POPULATIONS

The study population will consist of males and females with COPD, who have successfully completed study 042 or study 091 in accordance with the protocol. Patients who withdrew prior to completion of studies 042 or 091 are not eligible to enroll in study 040. Patients with positive faecal occult bloods at the end of the feeder studies, ongoing serious adverse experiences, ongoing gastrointestinal adverse experience or ongoing gastrointestinal clinically significant laboratory abnormalities were also not eligible for the study.

The population for analysis in this study will consist of all patients enrolled and confirmed to have received at least one dose of open-label study medication.

V. DATA ANALYSES

V.1 Efficacy Variables

- Pulmonary function tests (FEV₁, FEV₆, FEF₂₅₋₇₅, FEF₇₅, FVC, PEFR)
- Exercise tolerance test (6-minute walk test)
- Dyspnoea assessments (modified Borg scale) at rest to assess overall dyspnoea since the last visit and after exercise tolerance test
- COPD exacerbation rates
- Quality of life assessments
- Healthcare utilisation

V.2 Safety Parameters

- Adverse experiences including additional monitoring for gastrointestinal adverse experiences

- Laboratory safety data
- 12 lead ECG parameters
- Vital signs
- Physical examination including respiratory examination

V.3 Sample Size

No formal power calculations were performed since this is an open-label study with the primary purpose of evaluating patient safety. It is estimated that approximately 600 patients will be enrolled at 200 centres in Europe, South Africa and Australia/New Zealand participating in study 042 or study 091.

V.4 Efficacy analysis

The Biometrics Unit of SmithKline Beecham Pharmaceuticals will perform all statistical analyses.

Derivation of Efficacy Variables for Analysis

For each clinic pulmonary function parameter, three adequate readings will be collected at each scheduled evaluation. The highest of the three readings will be used in the analysis. If more than one set of readings is available for a particular assessment, the later of the two readings will be used in the analysis. For the SGRQ and SF-36 scores will be derived according to algorithms provided by the scales developers. Change from baseline will be calculated for all continuous efficacy parameters as the difference between the visit evaluation and the baseline evaluation. Baseline is defined as the predose evaluation at Visit 3 of the feeder study. For patients randomized to placebo in the feeder studies Change from Day 1 will also be calculated as the difference between the visit evaluation and the first day of dosing in study 040.

Comparisons of Interest

The primary comparison of interest will be the within group change from the baseline assessment of the feeder study (study 042 and study 091).

An additional comparison will be a within group change from Visit 1 of study 040 for patients randomized to placebo in the feeder study.

No comparison between the two groups will be performed.

Methods of Analysis

Descriptive statistics will be provided for all demographic and baseline characteristics.

For continuous efficacy endpoints, descriptive statistics (including mean, median, range, standard deviation and 95% confidence intervals) will be provided for the change from baseline at each scheduled study visit. No statistical hypothesis testing will be performed.

Annualised rates for COPD exacerbations and resource utilisation will be estimated using a Poisson regression model.

V.5 Safety Analysis

Evaluation of safety data will include all patients who receive at least one dose of study medication. Primary consideration will be given to presentation of the safety data without regard to randomized treatment in the feeder study. A secondary presentation of safety data will be by randomized treatment in the feeder study

Adverse experiences will be summarised by time to onset, severity, and Investigator-reported relationship of the adverse experience to study medication. Gastrointestinal adverse experiences of concern will be summarised separately. The proportion of patients withdrawn due to adverse experiences and due to gastrointestinal adverse experiences of concern will be evaluated.

For clinical laboratories, vital signs and ECG intervals descriptive statistics will be provided at each visit. For clinical laboratories the percentage of patients outside the normal limits and with values of sponsor-defined clinical concern will be tabulated across all on-therapy visits. Vital signs of clinical concern, orthostatic vital signs of clinical concern and ECGs of clinical concern will be tabulated in similar manner. Orthostatic vital signs of clinical concern will be summarised for all patients enrolled and the subgroup of patients with gastrointestinal adverse experiences of concern. Clinical concern criteria will be documented separately. In addition ECG abnormalities will be summarised using SNOMED terminology.

The proportion of patients with positive faecal occult bloods on-therapy will be tabulated for all enrolled patients and the subgroup of patients with gastrointestinal adverse experiences of concern.

Exploratory analyses will be performed to further characterise gastrointestinal adverse experiences of concern.

V.6 Data Handling Conventions

Pulmonary Function Tests

Repeat pulmonary function tests are defined as a set of 3 readings with an identical date and observation code to another set of 3 readings. In such cases the set of readings representing the later of the two times will be used for the analysis.

%Predicted FEV₁ will be calculated at entry of feeder studies and will be defined as :

$$\frac{100 * (\text{Post - bronchodilator FEV}_1)}{\text{Predicted FEV}_1}$$

Prediction equations for FEV₁ are provided in the protocol.

Salbutamol Reversibility will also be calculated at entry to the feeder studies and will be defined as:

$$\frac{[(\text{Post - bronchodilator FEV}_1) - (\text{Pre - bronchodilator FEV}_1)] * 100}{\text{Pre - bronchodilator FEV}_1}$$

The maximum pre and post-bronchodilator values will be used.

FEV₁/FVC ratio will also be calculated at entry to the feeder studies and defined as:

$$\frac{100 * \text{Pre - bronchodilator FEV}_1}{\text{Pre - bronchodilator FVC}}$$

The maximum Pre-bronchodilator FEV₁ and corresponding FVC will be used .

On-therapy early withdrawal visits will be analyzed as part of the LOCF analysis.

For each pulmonary function test (PFT) change from baseline will be defined at each visit as:

Maximum PFT at Visit – Maximum PFT at pre-dose assessment at baseline.

Study Medication Record

Compliance at each visit will be calculated and defined as:

$$\frac{100 \times \text{Number of tablets of study medication consumed}}{2 \times \text{Number of days between visits}}$$

where the number days between visits is defined as (Date of Current visit - Date of previous visit) and the number of tablets consumed is defined as the number dispensed minus the number returned minus the number lost.

For evening visits an additional half-day will be added to the number of days between visits. and one-half day subtracted from the number of days to the next visit.

Overall compliance will also be calculated and defined as:

$$100 * \frac{\sum \text{tablets consumed over double-blind period}}{2 * \text{Days of available compliance data on-therapy}}$$

where days of available compliance data on-therapy is defined as the total number of days for which compliance data was available during study 040.

Exposure to study medication will be defined without accounting for prior exposure in the feeder study. Exposure will be calculated as:

$$\text{Date of last dose in study 040} - \text{Date of first dose in study 040} + 1$$

An enrolled patient will be defined as any patient confirmed to have received open-label study medication in study 040.

Patients who were lost to follow up and for whom a first dose date is not available but have been confirmed to receive open-label study medication will have an assumed exposure of 1 day.

Adverse Experiences

An on-therapy adverse experience will be defined as any event with an onset date on or after the date of initial study 040 dose and prior to two days after the last dose of study medication in study 040.

A post-therapy adverse experience will be defined as any event with an onset date at least 2 days after the last dose of study medication.

An adverse experience leading to withdrawal will be defined as any on-therapy event where the "withdrawn" field is checked as "Yes".

Adverse events with missing onset dates will be assumed to be on-therapy with an onset on Day 1 of the open-label treatment period.

Visit Dates

The date for each visit will be defined as the date recorded on the Presentation to Clinic page of the CRF. If this date is not available the date on which the pulmonary function testing was performed will be used.

Concomitant and Prior Medications

A concomitant medication will be defined as any medication used following initial dose of study medication including continuing prior medications. Prior medications are defined as any medication used prior to visit 1 of study 040 including those which continued into study 040. Post-therapy medications are defined as any medication initiated after the last medication and does not include continuing medications from the active treatment period. Medications initiated on the last day of treatment will be classified as post-therapy medications.

Percent Predicted TLCO

Percent predicted TLCO will be calculated from the raw TLCO values collected at screening. The formula is:

$$\frac{100 * (\text{TLCO at screening})}{\text{Predicted TLCO}}$$

V.7 DMPK Evaluation

No plasma concentrations for Ariflo are being collected in this study.

V.8 Reports to be provided

Biometrics output required for the clinical report are fully described in the following mock-ups.

VI. VALUES OF CLINICAL CONCERN

The following vital signs and laboratory values defining levels of clinical concern were used to identify patients.

Laboratory Values of Interest and Potential Clinical Concern

Parameter	Low value of Concern	Low	High	High Value of Concern
Hemoglobin	< 0.8 x LLN	[0.8 x LLN - 1 x LLN)	(1 x LLN - 1.2 x LLN]	> 1.2 x ULN
Hematocrit	< 0.8 x LLN	[0.8 x LLN - 1 x LLN)	(1 x LLN - 1.2 x LLN]	> 1.2 x ULN
WBC	$\leq 3.0 \times 10^3/\text{mm}^3$	($3.0 \times 10^3/\text{mm}^3$ - 1 x LLN)	(1 x ULN - $20.0 \times 10^3/\text{mm}^3$)	$\geq 20.0 \times 10^3/\text{mm}^3$
Neutrophil (total)	< 0.8 x LLN	[0.8 x LLN - 1 x LLN)	(1 x LLN - 1.5 x LLN]	> 1.5 x ULN
Eosinophil	Not Defined	Not Defined	(1 x ULN - 2 x ULN]	> 2 x ULN
Platelet Count	< $100 \times 10^9/\text{L}$	[$100 \times 10^9/\text{L}$ - 1 x LLN)	(1 x ULN - $500 \times 10^9/\text{L}$]	> $500 \times 10^9/\text{L}$
AST (SGOT)	Not Defined	Not Defined	(1 x ULN - 2 x ULN]	> 2 x ULN
ALT (SGPT)	Not Defined	Not Defined	(1 x ULN - 2 x ULN]	> 2 x ULN
GGT	Not Defined	Not Defined	(1 x LLN - 2.5 x LLN]	> 2.5 x ULN
Total Bilirubin	Not Defined	Not Defined	(1 x LLN - 1.5 x LLN]	> 1.5 x ULN
Alkaline Phosphatase	Not Defined	Not Defined	(1 x ULN - 2 x ULN]	> 2.0 x ULN
Creatinine	< 0.5 x LLN	[0.5 x LLN - 1 x LLN)	(1 x LLN - 1.5 x LLN]	> 1.5 x ULN
BUN (SI Units)	Not Defined	Not Defined	(1 x ULN - 17.85 mmol/L]	> 17.85 mmol/L
(non SI Units)	Not Defined	Not Defined	(1 x ULN - 50 mg/dL]	> 50 mg/dL
Urea	Not Defined	Not Defined	(1 x ULN - 17.85 mmol/L]	> 17.85 mmol/L
Sodium (SI Units)	$\leq 130 \text{ mmol/L}$	(130 mmol/L - 1 x LLN)	(ULN - 150 mmol/L)	$\geq 150 \text{ mmol/L}$
(non-SI Units)	$\leq 130 \text{ mEq/L}$	(130 mEq/L - 1 x LLN)	(ULN - 150 mEq/L)	$\geq 150 \text{ mEq/L}$
Potassium (SI Units)	$\leq 3.0 \text{ mmol/L}$	(3.0 mmol/L - 1 x LLN)	(ULN - 5.5 mmol/L)	$\geq 5.5 \text{ mmol/L}$
(non-SI Units)	$\leq 3.0 \text{ mEq/L}$	(3.0 mEq/L - 1 x LLN)	(ULN - 5.5 mEq/L)	$\geq 5.5 \text{ mEq/L}$
Glucose (fasting/non-fasting)	< 2.0 mmol/L	[2.0 mmol/L - 1x LLN)	(ULN - 8.0 mmol/L]	> 8.0 mmol/L
Uric Acid	Not Defined	Not Defined	(ULN - 1.4 x ULN]	> 1.4 x ULN

LLN = Lower Limit of Normal; ULN = Upper Limit of Normal

(x - y) = value > x and $\leq$ y, [x - y) = value $\geq$ x and < y, (x - y) = value > x and < y

Vital Sign Levels of Interest and Potential Clinical Concern

Parameter	Low Concern	Low	High	High Concern
Sitting systolic BP	< 75 mm Hg	75 - 89 mm Hg	140 - 180 mm Hg	>180 mm Hg
Sitting diastolic BP	<50 mm Hg	50 - 59 mm Hg	90 - 110 mm Hg	> 110 mm Hg
Sitting heart rate	<50 bpm	50 - 59 bpm	100 - 120 bpm	> 120 bpm
Orthostatic change* in systolic BP	Not defined	Not defined	decrease of 10 - 19 mm Hg	decrease of $\geq$ 20 mm Hg
Orthostatic change* in diastolic BP	Not defined	Not defined	Not defined	decrease of $\geq$ 10 mm Hg
Orthostatic change* in heart rate	Not defined	Not defined	Not defined	increase of $\geq$ 10 bpm

*Orthostatic change assessed as change between supine for 5 minutes followed by sitting with legs dependent for 1 minute

Electrocardiographic Levels of Interest and Potential Clinical Concern

Parameter	Low Concern	Low	High	High Concern
QRS interval	Not defined	Not defined	120 - 199 msec	≥ 200 msec
PR interval	Not defined	Not defined	200 - 249 msec	≥ 250 msec
Atrial rate	< 50 bpm	50 - 59 bpm	100 - 120 bpm	> 120 bpm
Ventricular rate	< 50 bpm	50-59 bpm	100 - 120 bpm	> 120 bpm
Prolonged QT (corrected)	Not defined	Not defined	male 430 - 450 msec (borderline) female 450 – 470 msec (borderline)	male > 450 msec (prolonged) female > 470 msec (prolonged)
Prolonged QT (corrected) change from baseline	Not defined	Not defined	increase 30 – 60 msec	increase > 60 msec

VII. BAD LABORATORY VALUES

For those labs defined as "Lab Values of Concern" in Section VI, the definition encompasses values that fall below the defined low F3 or above the defined high F3. For those labs not included in Section VI, bad lab values are defined as <0.25LLN or >3ULN.

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Protocol	Centre Number	Patient Number	Patient Initials
207499/040			

CONFIDENTIAL



PROTOCOL SB 207499/040

BOOK 1 : VISITS 1 TO 4 (WEEK 0 TO 4)

**A MULTICENTRE, OPEN-LABEL EXTENSION STUDY
TO EVALUATE THE SAFETY, TOLERABILITY AND EFFICACY
OF ORAL SB 207499 (15mg TWICE DAILY) IN PATIENTS WITH
CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)**

GENERAL INSTRUCTIONS

- Write clearly in capital letters using a black ball point pen and press firmly so that all copies are legible
- Do not write in shaded areas
- Answer ALL questions on every page
- Enter "N/A" if information requested is not available
- Initial and date all changes, additions or deletions. Use a single pen stroke to remove an incorrect entry
- Enter the patient initials on all pages on which information has been entered and the patient number and centre number where required
- Do not enter additional data/information after the set of CRF pages has been split/separated
- The cover flap or plastic writing board should be used to divide each set of pages before writing on them with a ball point pen

DATE

Please use the following three-letter abbreviations for the months :

January	JAN
February	FEB
March	MAR
April	APR
May	MAY
June	JUN
July	JUL
August	AUG
September	SEP
October	OCT
November	NOV
December	DEC

e.g.

0	1	J	A	N	9	9
Day		Mth			Yr	

 = 1st January 1999

TIME

Unless specified otherwise, please use the 24 hour clock :

e.g.

1	5	3	0
24hr:min			

 = 3.30 p.m.

PATIENT INITIALS

Please use the following format ;

e.g. XXXXXXXXXX

ROUTE KEY FOR PRIOR/CONCOMITANT MEDICATION PAGE

PO = By mouth	SL = Sublingual	TD = Transdermal
IV = Intravenous	IT = Intrathecal	IH = Inhaled
IM = Intramuscular	VA = Vaginal	SC = Subcutaneous
IAR = Intra-arterial	NA = Nasal	PR = Rectal
TO = Topical	IA = Intra-articular injection	ID = Intradermal

SUMMARY CHART OF STUDY PROCEDURES (OPEN BOXES)
PROTOCOL SB 207499/040

Mark open boxes to confirm that each procedure has been completed.

Procedures	Visit 1	Visit 2	Visit 3	Visit 4
	Week 0	Week 1	Week 2	Week 4
Signed written informed consent				
Study Medication compliance				
Concomitant Medication	¹			
Diary Card Review ⁷	¹			
Adverse Experiences ⁸	¹			
COPD Exacerbation assessment/Healthcare Ut.	¹			
Physical (Including Respiratory) Examination	¹			
Resting 12-Lead ECG	¹			
Vital Signs (BP, HR) ³	¹			
Overall Breathlessness (Modified Borg)	¹			
Exercise Tolerance Test - 6 Minute Walk	¹			
Post Exercise Breathlessness	¹			
Pulmonary Function Tests ⁴	¹			
Laboratory Tests ⁵	¹			
Pregnancy Test ⁶	¹			
Quality of Life Assessment: SGRQ	¹			
Quality of Life Assessment: SF-36	¹			
Dispense or re-dispense Open-Label Medication				
Study Continuation / Withdrawal				

¹ Assessed during Visit 10, final double-blind visit of Study 042 or Visit 11 of Study 091 (except the QoL assessments for study 091 which are performed at Visit 10).

³ Orthostatic blood pressure and heart rate are measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal.

⁴ To include FEV₁, FEV₆, FVC, FEF₂₅₋₇₅, FEF₇₅, and PEF_R.

⁵ Faecal occult blood is measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal. Baseline measure is taken from last FOB in Study 042 or Study 091.

⁶ Serum pregnancy test for female patients of child bearing potential. Urine test only is done at Follow-Up Visit.

⁷ A Diary Card is issued at each visit. The patient will use the Diary Card to record if they feel differently since the previous visit.

⁸ Patients will be assessed for GI AEs at every visit.



Protocol 207499/040	Centre Number <table border="1"><tr><td></td><td></td><td></td></tr></table>				Patient Number <table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>								

MODULE 1

Module 1: Visit 1 to Visit 4, Adverse Experiences, Conmeds, Medical Procedures, COPD Exacerbations, Resource Utilisation, Study Continuation/Withdrawal.

CRF Pages: 1 - 54

Unprocessed forms: Within this module the following occur which will generate attachments that need to be brought in-house.

None



Page 1

Protocol	Centre Number	Patient Number	Patient Initials	Visit Date Day Mth Yr	Visit 1 Week 0
207499/040					

PREVIOUS STUDY

Please record the Study Number of the previous SB 207499 trial

Please record the Centre Number of the previous SB 207499 trial

Please record the Patient Number of the previous SB 207499 trial

INCLUSION/EXCLUSION CRITERIA**Complete the following inclusion/exclusion criteria****INCLUSION CRITERIA**

Yes No

1. Patient is male or female with COPD and has successfully completed study 042 or Study 091 where patient received SB 207499 15mg bid or placebo for 24 weeks in study 042 and 26 weeks in 091 without any tolerability problems. *Note : Women of childbearing potential must be using effective contraceptive measures (i.e. oral contraceptives, Norplant®, an IUD, a diaphragm with spermicide, a condom with spermicide, or Depo-Provera®) prior to Visit 1 and must continue using the same contraceptive measure during the study.*

☐
☐

2. Written informed consent obtained.

☐
☐
Do not admit the patient to this study if any "No" box has been marked**EXCLUSION CRITERIA**

Yes No

1. Patient is female and is pregnant or lactating, or is planning for pregnancy within the next 24 months.
2. Patient withdrew from study 042 or 091 for any reason.
3. Patient had a positive faecal occult blood test between Weeks 20 and 24 in study 042 or study 091.
4. Patient experienced a serious adverse experience, a gastrointestinal adverse experience or a clinically significant laboratory abnormality, which in the opinion of the Investigator could have been attributed to study medication during study 042 or study 091 and which is still present at the end of either study.
5. Patient is, in the opinion of the investigator, not suitable for enrolment into the study.

☐
☐
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☐
☐
Do not admit the patient to this study if any "Yes" box has been marked

I have assessed the patient and checked the inclusion/exclusion criteria above. The patient:

☐
is eligible to participate in the study.
☐
is not eligible to participate in the study.

I certify that I have reviewed the data on this case report form and that all information is complete and accurate.

Investigator's Signature _____

Date

Day Mth Yr



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 1 Week 0

INFORMED CONSENT

Date of informed consent

Day	Mth	Yr

ADVERSE EXPERIENCES

Please transcribe all adverse experiences which were ongoing at the end of the feeder study into the Adverse Experience section and ongoing COPD Exacerbations in the COPD Exacerbation section at the back of this module.

CONCOMITANT MEDICATION

Please transcribe all concomitant medications which were ongoing at the end of the feeder study into the Concomitant Medication section and ongoing concomitant medications for COPD in the COPD Exacerbation section at the back of this module.

STUDY MEDICATION LABEL

Issue the patient one bottle of open-label study medication (70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

Attach study medication
label here

For patients entering from study 091, give the patient the first morning dose of study medication with food and record the date and time of administration below. Remind the patient to take the first evening dose of study medication after their evening meal (at approximately 20:00).

For patients entering from study 042, remind the patient to take the first dose of open-label study medication with food at least 8 hours after the last dose of study 042 medication (at approximately 20:00) and to record the date and time of this dose in their diary. The date and time of the first dose should be transcribed from the patient's diary to the fields below at the patient's next visit.

Date and time of administration

Day	Mth	Yr	24hr:	min	

**PATIENT ENROLMENT FORM**
STUDY SB207499/040

Please complete this form and fax it to the local SB monitor

To :

Fax. No. :

The following patient has been enrolled in Study 207499/040 :

Patient Initials	Patient Number	Centre Number

Date enrolled :

Day	Mth	Yr

Signed : _____

Date :

Day	Mth	Yr

Please print name : _____

Institution : _____



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 1 Week 0

INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐ No —► If 'No' please complete the Study Continuation/withdrawal page at the back of this module.

☐ Yes —► If 'Yes' please;

- Issue the patient a diary card to be used by the patient to record if they feel differently since starting the study.
- Ask the patient to return for the next visit in 7 +/- 2 days.
- **Remind the patient:**
 - i to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.
 - ii **not** to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).
 - iii to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonists (long-acting) for **12 hours** before the next visit.
 - iv to refrain from smoking for **2 hours** immediately preceding the visit.
 - v to bring with them any remaining study medication or study medication containers and the diary card to the next visit.
 - vi to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]	Visit Date Day Mth Yr [][][][][]	Visit 2 Week 1

PRESENTATION TO CLINIC

Record time of presentation to clinic [][] 24hr:min

Record the date and time of the patient's last dose of short-acting beta₂ agonist [][] Day [][] Mth [][] Yr [][] 24hr:min

Record the date and time of the patient's last dose of long-acting beta₂ agonist [][] Day [][] Mth [][] Yr [][] 24hr:min

Record the date and time of the patient's last dose of anticholinergic [][] Day [][] Mth [][] Yr [][] 24hr:min

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes → If 'Yes' please record time [][] 24hr:min

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	[][] Day [][] Mth [][] Yr	[][] Day [][] Mth [][] Yr	[][] Day [][] Mth [][] Yr	[][] Day [][] Mth [][] Yr
Level of exacerbation (maximum intensity)	☐ Level 1	☐ Level 1	☐ Level 1	☐ Level 1
	☐ Level 2	☐ Level 2	☐ Level 2	☐ Level 2
	☐ Level 3	☐ Level 3	☐ Level 3	☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 2 Week 1

RESOURCE UTILISATION FOR COPD EXACERBATIONS

If the patient has received any COPD exacerbation related medical care since the previous visit, please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

*Review the diary card for illegible/incomplete entries **in the presence of the patient.***

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 2 Week 1

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)

Date and time of last dose of study medication prior to the study visit

Day	Mth	Yr	24hr:min		

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70					

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤ 120%?

☐ No —> If 'No' please emphasize the importance of compliance.

☐ Yes



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 2 Week 1

SMOKING STATUS

Does the patient currently smoke ?

☐

No

☐

Yes



If 'Yes' please record the average number of cigarettes per day :

PULMONARY REHABILITATION PROGRAMME

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit ?

☐

No

☐

Yes

LABORATORY TESTS

Please take blood samples for haematology and blood chemistry. Please refer to the instructions on the SBCL shipping form and manual.

Blood Sample Date

Day
Mth
Yr

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below.

Attach label here

Are there any **clinically significant worsenings** since the previous visit ?

☐

No

☐

Yes



If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

Place the SBCL laboratory report in the plastic wallet at the back of this module.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 2 Week 1

URINALYSIS

Please perform urinalysis using the dipstick provided by SBCL and record the results in the patient notes.

Urine Sample Date

Day
Mth
Yr

Are the dipstick results negative?

- ☐ No —▶ If 'No' please send the sample to SBCL for microscopy
- ☐ Yes

Are there any **clinically significant worsenings** since the last visit on the SBCL report ?

- ☐ No
- ☐ Yes —▶ If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 2 Week 1

INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)

Are there any **clinically significant worsenings** since the last visit ?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed:
Day Mth Yr

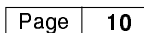
Were any clinically significant changes noted since the last visit ?

☐ No

☐ Yes → ☐ Improvement

☐ Worsening → *Enter details in the Adverse Experience section at the back of this module.*

Place the ECG trace in the plastic wallet at the back of this module.



Protocol		Patient Number	Patient Initials		Visit 2 Week 1
207499/040					

Re-issue the same supply of study medication issued at the previous visit. Record, in the next visit, the number of tablets reissued in the Study Medication Compliance section [Tablets Dispensed(X)] and todays date in the start date column in the Study Medication Record section.

Date and time of administration

Day	Mth	Yr	

24hr:min	

Is the patient continuing in the study?

- ☐ No → If 'No' please complete the assessments for Visit 2 and the Assessments for Patients Withdrawing or Stopping the Study at Visit 2 contained on the following pages. Complete and fax the Withdrawal Form contained in the Withdrawal and Follow-Up Book.
- ☐ Yes → If 'Yes' please;
- Issue a new diary card. Remind the patient to record if they feel differently since starting the study.
 - Ask the patient to return for the next visit in 7 +/- 2 days.
 - **Remind the patient:**
 - i to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.
 - ii **not** to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).
 - iii to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonists (long-acting) for **12 hours** before the next visit.
 - iv to refrain from smoking for **2 hours** immediately preceding the visit.
 - v to bring any remaining study medication or study medication containers and the diary card.
 - vi to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.



Protocol		Patient Number	Patient Initials		Visit 2 Week 1
207499/040					

ASSESSMENTS FOR PATIENTS WITHDRAWING OR STOPPING THE STUDY

Complete the assessments below only for patients who are withdrawing early from the study or stopping the study because the product has been registered or because the sponsor has terminated the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a clinically significant worsening in the patient's physical condition since the previous examination ?

☐

No

☐

Yes —> If 'Yes' record details in the Adverse Experience section at the back of this module.



Protocol 207499/040		Patient Number [][][][][]	Patient Initials [][][][]		Visit 2 Week 1

FAECAL OCCULT BLOOD TEST

Issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-Up Visit.

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement : After 5 Minutes Supine

Blood Pressure mmHg systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure mmHg systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the previous assessment ?

☐

No

☐

Yes



If 'Yes' record details in the Adverse Experience section at the back of this module.



Protocol		Patient Number	Patient Initials		Visit 2 Week 1
207499/040					

OVERALL BREATHLESSNESS ASSESSMENT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

PREGNANCY TEST

Is the patient a female of child-bearing potential ?

☐

No

☐

Yes

—▶ If 'Yes' please request a pregnancy test on the SBCL requisition form.

Is the patient pregnant?

☐

No

☐

Yes

—▶ If 'Yes' please enter details in the Adverse Experience section.



Protocol		Patient Number	Patient Initials		Visit 2 Week 1
207499/040					

PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and / or anticholinergic medications and / or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Follow-Up Visit in 7 +/- 3 days.



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Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]	Visit Date Day Mth Yr [][][][][]	Visit 3 Week 2

PRESENTATION TO CLINIC

Record time of presentation to clinic [][][]
24hr:min

Note: Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.

Record the date and time of the patient's last dose of short-acting beta₂ agonist [][][][][][] 24hr:min
Day Mth Yr

Record the date and time of the patient's last dose of long-acting beta₂ agonist [][][][][][] 24hr:min
Day Mth Yr

Record the date and time of the patient's last dose of anticholinergic [][][][][][] 24hr:min
Day Mth Yr

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes → If 'Yes' please record time [][][] 24hr:min

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	[][][][][][] Day Mth Yr	[][][][][][] Day Mth Yr	[][][][][][] Day Mth Yr	[][][][][][] Day Mth Yr
Level of exacerbation (maximum intensity)	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 3 Week 2

RESOURCE UTILISATION FOR COPD EXACERBATIONS

If the patient has received any COPD exacerbation related medical care since the previous visit, please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

*Review the diary card for illegible/incomplete entries **in the presence of the patient.***

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 3 Week 2

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication redispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)

Date and time of last dose of study medication prior to the study visit

Day Mth Yr

24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Redispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤ 120%?

- ☐ No → If 'No' please check the % compliance at the previous visit. If compliance was not ≥ 80% and ≤ 120% at the last visit, please withdraw the patient. Please complete the assessments for Visit 3 and the assessments for patients withdrawing or stopping the study at Visit 3, contained at the end of this visit.
- ☐ Yes



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 3 Week 2

SMOKING STATUS

Does the patient currently smoke ?

☐

No

☐

Yes



If 'Yes' please record the average number of cigarettes per day :

PULMONARY REHABILITATION PROGRAMME

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit ?

☐

No

☐

Yes

LABORATORY TESTS

Please take blood samples for haematology and blood chemistry. Please refer to the instructions on the SBCL shipping form and manual.

Blood Sample Date

Day
Mth
Yr

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below.

Attach label here

Are there any **clinically significant worsenings** since the previous visit ?

☐

No

☐

Yes



If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

Place the SBCL laboratory report in the plastic wallet at the back of this module.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 3 Week 2

URINALYSIS

Please perform urinalysis using the dipstick provided by SBCL and record the results in the patient notes.

Urine Sample Date / /
Day Mth Yr

Are the dipstick results negative?

- ☐ No —▶ If 'No' please send the sample to SBCL for microscopy
☐ Yes

Are there any **clinically significant worsenings** since the last visit on the SBCL report?

- ☐ No
☐ Yes —▶ If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

OVERALL BREATHLESSNESS ASSESSMENT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 3 Week 2

INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)

Are there any **clinically significant worsenings** since the last visit ?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed:
Day Mth Yr

Were any clinically significant changes noted since the last visit ?

☐ No

☐ Yes → ☐ Improvement

☐ Worsening → *Enter details in the Adverse Experience section at the back of this module.*

Place the ECG trace in the plastic wallet at the back of this module.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 3 Week 2

PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and / or anticholinergic medications and / or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

STUDY MEDICATION RE-ISSUE

Re-issue the same supply of study medication issued at the previous visit. Record, in the next visit, the number of tablets reissued in the Study Medication Compliance section [Tablets Dispensed(X)] and today's date in the start date column in the Study Medication Record section.

Give the patient the next dose of study medication with food and record the date and time of administration below.

Date and time of administration
Day Mth Yr 24hr:min



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 3 Week 2

INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐ No —► If 'No' please complete the assessments for Visit 3 and the Assessments for Patients Withdrawing or Stopping the Study at Visit 3 contained on the following pages. Complete and fax the Withdrawal Form contained in the Withdrawal and Follow-Up Book.

☐ Yes —► If 'Yes' please;

- Issue a new diary card. Remind the patient to record if they feel differently since starting the study.
- Ask the patient to return for the next visit in 14 +/- 3 days.
- **Remind the patient:**
 - i to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.
 - ii **not** to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).
 - iii to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonists (long-acting) for **12 hours** before the next visit.
 - iv to refrain from smoking for **2 hours** immediately preceding the visit.
 - v to bring any remaining study medication or study medication containers and the diary card to the next visit.
 - vi to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.



Protocol		Patient Number	Patient Initials		Visit 3 Week 2
207499/040					

ASSESSMENTS FOR PATIENTS WITHDRAWING OR STOPPING THE STUDY

Complete the assessments below only for patients who are withdrawing early from the study or stopping the study because the product has been registered or because the sponsor has terminated the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a clinically significant worsening in the patient's physical condition since the previous examination ?

☐

No

☐

Yes



If 'Yes' record details in the Adverse Experience section at the back of this module.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 3 Week 2

FAECAL OCCULT BLOOD TEST

Issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-Up Visit.

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement : After 5 Minutes Supine

Blood Pressure mmHg systolic / diastolic	Heart Rate beats/min
/	

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure mmHg systolic / diastolic	Heart Rate beats/min
/	

Are there any **clinically significant worsenings** since the previous assessment ?

☐

No

☐

Yes



If 'Yes' record details in the Adverse Experience section at the back of this module.



Protocol 207499/040		Patient Number <table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>						Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						Visit 3 Week 2

PREGNANCY TEST

Is the patient a female of child-bearing potential ?

☐

No

☐

Yes



If 'Yes' please request a pregnancy test on the SBCL requisition form.

Is the patient pregnant?

☐

No

☐

Yes



If 'Yes' please enter details in the Adverse Experience section.

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Follow-Up Visit in 7 +/- 3 days.



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Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]	Visit Date Day Mth Yr [][][][][]	Visit 4 Week 4

PRESENTATION TO CLINIC

Record time of presentation to clinic [][][]
24hr:min

Note: Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.

Record the date and time of the patient's last dose of short-acting beta₂ agonist [][][][][][] 24hr:min
Day Mth Yr

Record the date and time of the patient's last dose of long-acting beta₂ agonist [][][][][][] 24hr:min
Day Mth Yr

Record the date and time of the patient's last dose of anticholinergic [][][][][][] 24hr:min
Day Mth Yr

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes → If 'Yes' please record time [][][] 24hr:min

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	[][][][][][] Day Mth Yr	[][][][][][] Day Mth Yr	[][][][][][] Day Mth Yr	[][][][][][] Day Mth Yr
Level of exacerbation (maximum intensity)	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 4 Week 4

RESOURCE UTILISATION FOR COPD EXACERBATIONS

Please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

Review the diary card for illegible/incomplete entries **in the presence of the patient**.

ADVERSE EXPERIENCES

Please complete the Adverse Experience section at the back of this module. If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

Please complete the Concomitant Medication section at the back of this module. If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 4 Week 4

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)

Date and time of last dose of study medication prior to the study visit

Day Mth Yr

24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Redispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤ 120%?

- ☐ No → If 'No' please check the % compliance at the previous visit. If compliance was not ≥ 80% and ≤ 120% at the last visit, please withdraw the patient. Please complete the assessments for Visit 4 and the assessments for patients withdrawing or stopping the study at Visit 4, contained at the end of this visit.
- ☐ Yes



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 4 Week 4

SMOKING STATUS

Does the patient currently smoke ?

☐

No

☐

Yes



If 'Yes' please record the average number of cigarettes per day :

PULMONARY REHABILITATION PROGRAMME

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit ?

☐

No

☐

Yes

LABORATORY TESTS

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential). Please refer to the instructions on the SBCL shipping form and manual.

Blood Sample Date

Day
Mth
Yr

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below.

Attach label here

Are there any **clinically significant worsenings** since the previous visit ?

☐

No

☐

Yes



If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

Place the SBCL laboratory report in the plastic wallet at the back of this module.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 4 Week 4

URINALYSIS

Please perform urinalysis using the dipstick provided by SBCL and record the results in the patient notes.

Urine Sample Date
Day Mth Yr

Are the dipstick results negative?

- ☐ No —▶ If 'No' please send the sample to SBCL for microscopy
☐ Yes

Are there any **clinically significant worsenings** since the last visit on the SBCL report?

- ☐ No
☐ Yes —▶ If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

PREGNANCY TEST

Is the patient a female of child-bearing potential ?

- ☐ No
☐ Yes —▶ If 'Yes' please request a pregnancy test on the SBCL requisition form.

Is the patient pregnant?

- ☐ No
☐ Yes —▶ If 'Yes' please withdraw the patient from the study, enter details in the Adverse Experience section. Complete the Early Withdrawal Visit (found in a separate book).



Protocol 207499/040		Patient Number <table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>						Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						Visit 4 Week 4

OVERALL BREATHLESSNESS ASSESSMENT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 4 Week 4

INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)

Are there any **clinically significant worsenings** since the last visit ?

☐

No

☐

Yes



If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed:

Day	Mth	Yr	

Were any clinically significant changes noted since the last visit ?

☐

No

☐

Yes


☐

Improvement

☐

Worsening



Enter details in the Adverse Experience section at the back of this module.

Place the ECG trace in the plastic wallet at the back of this module.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 4 Week 4

PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and / or anticholinergic medications and / or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

STUDY MEDICATION LABEL

Issue the patient one bottle of open-label study medication (70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

Attach study medication
label here

Give the patient the first dose of study medication with food and record the date and time of administration below.

Date and time of administration

Day	Mth	Yr	24hr:min		



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 4 Week 4

INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐ No —► If 'No' please complete the assessments for Visit 4 and the Assessments for Patients Withdrawing or Stopping the Study at Visit 4 contained on the following pages. Complete and fax the Withdrawal Form contained in the Withdrawal and Follow-Up Book.

☐ Yes —► If 'Yes' please;

- Issue a new diary card. Remind the patient to record if they feel differently since starting the study.
- Ask the patient to return for the next visit in 28 +/- 6 days.
- Complete the Study Continuation / Withdrawal page at the back of this module.
- **Remind the patient:**
 - i to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.
 - ii **not** to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).
 - iii to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonists (long-acting) for **12 hours** before the next visit.
 - iv to refrain from smoking for **2 hours** immediately preceding the visit.
 - v to bring any remaining study medication or study medication containers and the diary card.
 - vi to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 4 Week 4

ASSESSMENTS FOR PATIENTS WITHDRAWING OR STOPPING THE STUDY

Complete the assessments below only for patients who are withdrawing early from the study or stopping the study because the product has been registered or because the sponsor has terminated the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a clinically significant worsening in the patient's physical condition since the previous examination ?

☐

No

☐

Yes



If 'Yes' record details in the Adverse Experience section at the back of this module.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 4 Week 4

FAECAL OCCULT BLOOD TEST

Issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-Up Visit.

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement : After 5 Minutes Supine

Blood Pressure mmHg systolic / diastolic	Heart Rate beats/min

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure mmHg systolic / diastolic	Heart Rate beats/min

Are there any **clinically significant worsenings** since the previous assessment ?

☐

No

☐

Yes



If 'Yes' record details in the Adverse Experience section at the back of this module.

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Follow-Up Visit in 7 +/- 3 days.

ADVERSE EXPERIENCES (Non-serious)**DEFINITIONS****INTENSITY (Maximum)**

MILD	<i>Adverse experience which is easily tolerated</i>
MODERATE	<i>Adverse experience sufficiently discomforting to interfere with daily activity</i>
SEVERE	<i>Adverse experience which prevents normal everyday activities</i>

RELATIONSHIP TO INVESTIGATIONAL DRUG

NOT RELATED	<i>The adverse experience is definitely not related to the test drug</i>
UNLIKELY	<i>There are other more likely causes and the drug is not suspected as a cause</i>
SUSPECTED (REASONABLE POSSIBILITY)	<i>A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug</i>
PROBABLE	<i>There probably is a direct cause and effect relationship between the adverse experience and the study drug</i>

SERIOUS ADVERSE EXPERIENCE (SAE)

A SAE is any experience which is :-

- 1 - fatal
- 2 - life threatening
- 3 - disabling/incapacitating
- 4 - results in hospitalisation (excluding elective surgery or routine clinical procedures)
- 5 - prolongs a hospital stay
- 6 - associated with congenital abnormality
- 7 - cancer
- 8 - associated with overdose
- 9 - In addition any event which the investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug should be reported as a serious event

IF A SAE OCCURS, PLEASE GO TO THE SAE SECTION IMMEDIATELY AND FOLLOW THE INSTRUCTIONS GIVEN THERE

Use each form for a maximum of two experiences

PLEASE REMEMBER ALL QUESTIONS ON ADVERSE EXPERIENCES FORM SHOULD BE COMPLETED



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Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Please record all AEs ongoing at the end of the feeder study in this section.

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Do you feel different in any way since starting the treatment or since the previous study?" Provide the diagnosis **not** symptoms where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbation section.

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the SAE section (See opposite for definitions of an SAE).

If no ongoing or new adverse experiences occurred since the previous study, please sign form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Mth Yr 24hr:min	 Day Mth Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Mth Yr 24hr:min	 Day Mth Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy <i>If 'Yes', record details in the Concomitant Medication and / or Medical Procedures section</i> ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE ?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Mth Yr	



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Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Please record all AEs ongoing at the end of the feeder study in this section.

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Do you feel different in any way since starting the treatment or since the previous study?" Provide the diagnosis **not** symptoms where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbation section.

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the SAE section (See opposite for definitions of an SAE).

If no further adverse experiences or changes in adverse experiences occurred since the previous study, please sign form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Mth Yr 24hr:min	 Day Mth Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Mth Yr 24hr:min	 Day Mth Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy <i>If 'Yes', record details in the Concomitant Medication and / or Medical Procedures section</i> ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE ?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Mth Yr	



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Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Please record all AEs ongoing at the end of the feeder study in this section.

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Do you feel different in any way since starting the treatment or since the previous study?" Provide the diagnosis **not** symptoms where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbation section.

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the SAE section (See opposite for definitions of an SAE).

If no further adverse experiences or changes in adverse experiences occurred since the previous study, please sign form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Mth Yr 24hr:min	 Day Mth Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Mth Yr 24hr:min	 Day Mth Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy <i>If 'Yes', record details in the Concomitant Medication and / or Medical Procedures section</i> ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE ?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Mth Yr	



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Protocol	Centre Number	Patient Number	Patient Initials		
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CONCOMITANT MEDICATION

Please transcribe all concomitant medications which were ongoing at the end of the feeder study. Record any changes in concomitant medication taken since the previous study. (Please write using BLOCK CAPITALS)

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

☐ No concomitant medication changes since the previous study and no ongoing medication

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experience section using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the start and end date.

Drug Name (Trade name preferred)	Unit Dose (e.g. 500mg)	Frequency (e.g. bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of a diagnosis)	Start Date (be as precise as possible) Day Mth Yr	End Date (or if continuing mark box) Day Mth Yr	
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* For Route, see tab for acceptable abbreviations.



Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

CONCOMITANT MEDICATION - Continued

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experience section using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the start and end date.

Drug Name (Trade name preferred)	Unit Dose (e.g. 500mg)	Frequency (e.g. bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of a diagnosis)	Start Date (be as precise as possible)			End Date (or if continuing mark box)		
					Day	Mth	Yr	Day	Mth	Yr
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* For Route, see tab for acceptable abbreviations.



Protocol	Centre Number	Patient Number	Patient Initials	Visit Date	
207499/040				Day Mth Yr	

MEDICAL PROCEDURES (Excluding treatment for COPD exacerbations)

Do not record procedures used to treat COPD exacerbations here, record them in the COPD Exacerbations section.

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed since the previous study ?

☐ No

☐ Yes —▶ If 'Yes', please record details below using standard medical terminology

All indications for procedures should be recorded in the Adverse Experience section.

Procedure	Indication	Procedure Start Date			Procedure End Date		
		Day	Mth	Yr	Day	Mth	Yr
For SB							
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For SB							
For SB							
For SB							
For SB							
For SB							
For SB							



Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

Please record all COPD exacerbations ongoing at the end of the feeder study in this section. An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy. All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages.**

If no ongoing or new COPD Exacerbations since the previous study, please sign form below and mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	 Day Mth Yr 24hr:min	 Day Mth Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Mth Yr 24hr:min	 Day Mth Yr 24hr:min
Outcome If patient died, STOP: go to SAE COPD Exacerbation pages	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent ☐ Constant	☐ Intermittent ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Concomitant Medication and/or Medical Procedures section	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE ?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Mth Yr	



Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

Please record all COPD exacerbations ongoing at the end of the feeder study in this section. An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy. All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages.**

If no further COPD Exacerbations or changes to COPD Exacerbations have occurred since the previous study, please sign form below and mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
End Date and Time (If ongoing please leave blank)	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
Outcome If patient died, STOP: go to SAE COPD Exacerbation pages	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent ☐ No. of episodes ☐ Constant	☐ Intermittent ☐ No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Concomitant Medication and / or Medical Procedures section	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE ?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Mth Yr	



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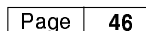
Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

Please record all COPD exacerbations ongoing at the end of the feeder study in this section. An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy. All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages.**

If no further COPD Exacerbations or changes to COPD Exacerbations have occurred since the previous study, please sign form below and mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
End Date and Time (If ongoing please leave blank)	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
Outcome If patient died, STOP: go to SAE COPD Exacerbation pages	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent ☐ Constant	☐ Intermittent ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Concomitant Medication and/or Medical Procedures section	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE ?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Mth Yr	



Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date
207499/040				Day Mth Yr

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience	COPD Exacerbation	➤ Specify reason(s) for considering this a serious AE. Mark all that apply. 1 2 3 4 5 6 7 8 9 ☐ fatal ☐ life threatening ☐ disabling/incapacitating ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) ☐ hospitalisation prolonged ☐ congenital abnormality ☐ cancer ☐ overdose ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	Day Mth Yr 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	Day Mth Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent ➤ No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate ? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased) ☐ Yes ☐ No If yes, did SAE recur ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	➤ Assessment The SAE is probably associated with : ☐ Protocol design or procedures (but not to study drug) <i>Please specify</i> _____ ☐ Another condition (eg, condition under study, intercurrent illness) <i>Please specify</i> _____ ☐ Another drug <i>Please specify</i> _____
Corrective Therapy <i>If 'Yes', record details in the COPD Medication or Procedures pages</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)

Relevant Laboratory Data

Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

If applicable, was randomisation code broken at investigational site ? ☐ No ☐ Yes

Randomisation / Study Medication Number : [][][][][]

Investigator's Signature : _____ **Date**

Day Mth Yr

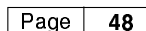
(confirming that the above data are accurate and complete)

Please PRINT name _____

SB Medical Monitor's Signature : _____ **Date**

Day Mth Yr

Please PRINT name _____



Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date
207499/040				Day Mth Yr

Person Reporting SAE _____ (Please print clearly)		AEGIS Number . 	
Serious Adverse Experience		COPD Exacerbation	
For SmithKline Beecham		➤ Specify reason(s) for considering this a serious AE. Mark all that apply.	
Onset Date and Time	Day Mth Yr 24hr:min	1 ☐ fatal	
End Date and Time (If ongoing please leave blank)	Day Mth Yr 24hr:min	2 ☐ life threatening	
Outcome If patient died, please complete Form D	☐ Resolved ☐ Ongoing ☐ Died	3 ☐ disabling/incapacitating	
Experience Course	☐ Intermittent ➤ No. of episodes ☐ Constant	4 ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures)	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	5 ☐ hospitalisation prolonged	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	6 ☐ congenital abnormality	
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	7 ☐ cancer	
Corrective Therapy If 'Yes', record details in the COPD Medication or Procedures pages	☐ Yes ☐ No	8 ☐ overdose	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	9 ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution	



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)

Relevant Laboratory Data

Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

If applicable, was randomisation code broken at investigational site ? ☐ No ☐ Yes

Randomisation / Study Medication Number : [][][][][]

Investigator's Signature : _____ **Date**

Day Mth Yr

(confirming that the above data are accurate and complete)

Please PRINT name _____

SB Medical Monitor's Signature : _____ **Date**

Day Mth Yr

Please PRINT name _____



Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

MEDICATION FOR COPD EXACERBATIONS

Please transcribe all medications for COPD exacerbations ongoing at the end of the feeder study.

Has the patient taken any medication for COPD exacerbations since the previous study ?

☐ No

☐ Yes → If 'Yes', please record details below

Drug Name (Trade name preferred)	Unit Dose (e.g. 500mg)	Frequency (e.g. bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of a diagnosis)	Start Date (be as precise as possible)			End Date (or if continuing mark box)		
					Day	Mth	Yr	Day	Mth	Yr
				COPD EXACERBATION						
For SB										
				COPD EXACERBATION						
For SB										
				COPD EXACERBATION						
For SB										
				COPD EXACERBATION						
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				COPD EXACERBATION						
For SB										
				COPD EXACERBATION						
For SB										
				COPD EXACERBATION						
For SB										

* For Route, see General Instructions for acceptable abbreviations.



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]		

MEDICAL PROCEDURES FOR COPD EXACERBATIONS

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since the previous study ?

☐ No

☐ Yes —▶ If 'Yes', please record details below using standard medical terminology

Procedure	Indication	Procedure Start Date			Procedure End Date		
		Day	Mth	Yr	Day	Mth	Yr
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							

Protocol 207499/040	Centre Number [][][][]	Patient Number [][][][][][]	Patient Initials [][][][][]		

COPD RESOURCE UTILISATION

Complete this form for any **COPD exacerbation related medical care** the patient received since the previous study

Physician Visits (i.e., COPD care excluding scheduled protocol visits)

☐ There were no physician visits since the previous study

Date of Visit Day Mth Yr	Reason for Visit
[][][][][][]	
[][][][][][]	
[][][][][][]	
[][][][][][]	
[][][][][][]	
[][][][][][]	
[][][][][][]	
[][][][][][]	
[][][][][][]	

Emergency Room (ER)/Urgent Care Visits/Casualty Department Procedures (i.e., lung surgery)

☐ There were no Emergency Room/Urgent Care Visits/Casualty Department Procedures since previous study

Date of Visit Day Mth Yr	Reason for Visit	Patient Admitted from ER ?	
		Yes	No
[][][][][][]		☐	☐
[][][][][][]		☐	☐
[][][][][][]		☐	☐
[][][][][][]		☐	☐
[][][][][][]		☐	☐
[][][][][][]		☐	☐
[][][][][][]		☐	☐
[][][][][][]		☐	☐



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]		

COPD RESOURCE UTILISATION - Continued

Hospitalisations (also record details of any hospitalisations in the Serious Adverse Experience - COPD Exacerbation section)

☐ There were no hospitalisations since the previous study

Date of Admission			Date of Discharge			Reason for Admission
Day	Mth	Yr	Day	Mth	Yr	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	

Intensive Care Unit (ICU) stays (did the patient stay in the ICU during any of the above hospitalisations?)

☐ There were no ICU stays since the previous study

Date Admitted to ICU			Date Discharged from ICU			Reason for ICU Admission
Day	Mth	Yr	Day	Mth	Yr	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	

Lost Work Days (i.e., days patient missed work due to COPD excluding scheduled protocol visits)

☐ There were no lost work days since the previous study

Start Date			Stop Date			Reason for Absence
Day	Mth	Yr	Day	Mth	Yr	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	



Protocol	Centre Number	Patient Number	Patient Initials		
207499/040					

STUDY CONTINUATION / WITHDRAWAL

Is the patient continuing in the study ?

☐ Yes

☐ No —→ If 'No' please mark the **PRIMARY** cause of withdrawal and enter the date of the final visit and the date of the final dose.

1	☐ Adverse experience (complete AE form)
2	☐ Insufficient therapeutic effect
3	☐ Protocol deviation (including non-compliance)
4	☐ Lost to follow-up
5	☐ Other - specify:

Date of Final Visit
Day Mth Yr

Date of Final Dose
Day Mth Yr

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data on this case report form and that all information is complete and accurate.

Investigator's Signature Date
Day Mth Yr

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)

SAEs MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS

COMPLETE THE SAE PAGES OPPOSITE

Please complete these pages as fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Experience Course' blank and update it later

SIGN AND DATE THE SAE PAGE**PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE**

- Demography
- Significant Medical/Surgical History and Physical Examination
- Study Medication Record
- Concomitant Medication
- Form D (if applicable)

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE

(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO :

Your local SB CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local SB CRA/Medical monitor within 24 hours



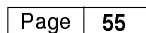
Protocol 207499/040	Centre Number <table border="1"><tr><td></td><td></td><td></td></tr></table>				Patient Number <table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>								

MOD2 & MOD3 - SERIOUS ADVERSE EXPERIENCES

MOD2 & 3: Serious Adverse Experiences

MOD2 : 55, 56

MOD3 : 57, 58



Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date
207499/040				DayMthYr

Person Reporting SAE _____ (Please print clearly)		AEGIS Number <table border="1" style="display: inline-table; width: 100px; height: 20px; vertical-align: middle;"></table> . <table border="1" style="display: inline-table; width: 20px; height: 20px; vertical-align: middle;"></table>																												
Serious Adverse Experience (Please print clearly)		➔ Specify reason(s) for considering this a serious AE. Mark all that apply. <table border="0" style="width: 100%;"> <tr><td>1</td><td>☐</td><td>fatal</td></tr> <tr><td>2</td><td>☐</td><td>life threatening</td></tr> <tr><td>3</td><td>☐</td><td>disabling/incapacitating</td></tr> <tr><td>4</td><td>☐</td><td>results in hospitalisation (excluding elective surgery or routine clinical procedures)</td></tr> <tr><td>5</td><td>☐</td><td>hospitalisation prolonged</td></tr> <tr><td>6</td><td>☐</td><td>congenital abnormality</td></tr> <tr><td>7</td><td>☐</td><td>cancer</td></tr> <tr><td>8</td><td>☐</td><td>overdose</td></tr> <tr><td>9</td><td>☐</td><td>Investigator considers serious or a significant hazard, contraindication, side effect or precaution</td></tr> </table>		1	☐	fatal	2	☐	life threatening	3	☐	disabling/incapacitating	4	☐	results in hospitalisation (excluding elective surgery or routine clinical procedures)	5	☐	hospitalisation prolonged	6	☐	congenital abnormality	7	☐	cancer	8	☐	overdose	9	☐	Investigator considers serious or a significant hazard, contraindication, side effect or precaution
1	☐			fatal																										
2	☐			life threatening																										
3	☐			disabling/incapacitating																										
4	☐			results in hospitalisation (excluding elective surgery or routine clinical procedures)																										
5	☐	hospitalisation prolonged																												
6	☐	congenital abnormality																												
7	☐	cancer																												
8	☐	overdose																												
9	☐	Investigator considers serious or a significant hazard, contraindication, side effect or precaution																												
For SmithKline Beecham																														
Onset Date and Time	<table border="1" style="display: inline-table; width: 40px; height: 20px; vertical-align: middle;"></table> <table border="1" style="display: inline-table; width: 40px; height: 20px; vertical-align: middle;"></table> <table border="1" style="display: inline-table; width: 40px; height: 20px; vertical-align: middle;"></table> <table border="1" style="display: inline-table; width: 40px; height: 20px; vertical-align: middle;"></table> Day Mth Yr 24hr:min																													
End Date and Time (If ongoing please leave blank)	<table border="1" style="display: inline-table; width: 40px; height: 20px; vertical-align: middle;"></table> <table border="1" style="display: inline-table; width: 40px; height: 20px; vertical-align: middle;"></table> <table border="1" style="display: inline-table; width: 40px; height: 20px; vertical-align: middle;"></table> <table border="1" style="display: inline-table; width: 40px; height: 20px; vertical-align: middle;"></table> Day Mth Yr 24hr:min																													
Outcome If patient died, please complete Form D	☐ Resolved ☐ Ongoing ☐ Died																													
Experience Course	☐ Intermittent ➔ No. of <table border="1" style="display: inline-table; width: 40px; height: 20px; vertical-align: middle;"></table> ☐ Constant episodes																													
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe																													
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped																													
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable																													
Corrective Therapy If 'Yes', record details in the Concomitant Medication section	☐ Yes ☐ No																													
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No																													



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data**

Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

If applicable, was randomisation code broken at investigational site ? ☐ No ☐ Yes

Randomisation / Study Medication Number : [][][][][]

Investigator's Signature : _____ **Date**

Day Mth Yr

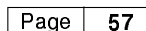
(confirming that the above data are accurate and complete)

Please PRINT name _____

SB Medical Monitor's Signature : _____ **Date**

Day Mth Yr

Please PRINT name _____



Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date
207499/040				DayMthYr

Person Reporting SAE _____ (Please print clearly)		AEGIS Number . 	
Serious Adverse Experience (Please print clearly)	➤ Specify reason(s) for considering this a serious AE. Mark all that apply.		
For SmithKline Beecham	1 ☐ fatal 2 ☐ life threatening 3 ☐ disabling/incapacitating 4 ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) 5 ☐ hospitalisation prolonged 6 ☐ congenital abnormality 7 ☐ cancer 8 ☐ overdose 9 ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution		
Onset Date and Time			
End Date and Time (If ongoing please leave blank)			
Outcome If patient died, please complete Form D	☐ Resolved ☐ Ongoing ☐ Died		
Experience Course	☐ Intermittent ➤ No. of episodes ☐ Constant		
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe		
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped		
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable		
Corrective Therapy If 'Yes', record details in the Concomitant Medication section	☐ Yes ☐ No		
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No		

Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 	

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data**

Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	 Day Mth Yr			
	 Day Mth Yr			
	 Day Mth Yr			
	 Day Mth Yr			

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

If applicable, was randomisation code broken at investigational site ? ☐ No ☐ Yes

Randomisation / Study Medication Number :

Investigator's Signature : _____ **Date**
 (confirming that the above data are accurate and complete)

Please PRINT name _____

SB Medical Monitor's Signature : _____ **Date**
 (confirming that the above data are accurate and complete)

Please PRINT name _____

Protocol	Centre Number	Patient Number	Patient Initials
207499/040			

CONFIDENTIAL



PROTOCOL SB 207499/040

BOOK 2 : VISITS 5 AND 6 (WEEKS 8 AND 12)

**A MULTICENTRE, OPEN-LABEL EXTENSION STUDY
TO EVALUATE THE SAFETY, TOLERABILITY AND EFFICACY
OF ORAL SB 207499 (15mg TWICE DAILY) IN PATIENTS WITH
CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)**

GENERAL INSTRUCTIONS

- Write clearly in capital letters using a black ball point pen and press firmly so that all copies are legible
- Do not write in shaded areas
- Answer ALL questions on every page
- Enter "N/A" if information requested is not available
- Initial and date all changes, additions or deletions. Use a single pen stroke to remove an incorrect entry
- Enter the patient initials on all pages on which information has been entered and the patient number and centre number where required
- Do not enter additional data/information after the set of CRF pages has been split/separated
- The cover flap or plastic writing board should be used to divide each set of pages before writing on them with a ball point pen

DATE

Please use the following three-letter abbreviations for the months :

January	JAN
February	FEB
March	MAR
April	APR
May	MAY
June	JUN
July	JUL
August	AUG
September	SEP
October	OCT
November	NOV
December	DEC

e.g.

0	1	J	A	N	9	9
Day		Mth			Yr	

 = 1st January 1999

TIME

Unless specified otherwise, please use the 24 hour clock :

e.g.

1	5	3	0
24hr		min	

 = 3.30 p.m.

PATIENT INITIALS

Please use the following format ;

e.g. XXXXXXXXXX

ROUTE KEY FOR PRIOR/CONCOMITANT MEDICATION PAGE

PO = By mouth	SL = Sublingual	TD = Transdermal
IV = Intravenous	IT = Intrathecal	IH = Inhaled
IM = Intramuscular	VA = Vaginal	SC = Subcutaneous
IAR = Intra-arterial	NA = Nasal	PR = Rectal
TO = Topical	IA = Intra-articular injection	ID = Intradermal

SUMMARY CHART OF STUDY PROCEDURES (OPEN BOXES)
PROTOCOL SB 207499/040

Mark open boxes to confirm that each procedure has been completed.

Procedures	Visit 5	Visit 6
	Week 8	Week 12
Signed written informed consent		
Study Medication compliance		
Concomitant Medication		
Diary Card Review ⁷		
Adverse Experiences ⁸		
COPD Exacerbation assessment/Healthcare Ut.		
Physical (Including Respiratory) Examination		
Resting 12-Lead ECG		
Vital Signs (BP, HR) ³		
Overall Breathlessness (Modified Borg)		
Exercise Tolerance Test - 6 Minute Walk		
Post Exercise Breathlessness		
Pulmonary Function Tests ⁴		
Laboratory Tests ⁵		
Pregnancy Test ⁶		
Quality of Life Assessment: SGRQ		
Quality of Life Assessment: SF-36		
Dispense or re-dispense Open-Label Medication		
Study Continuation / Withdrawal		

³ Orthostatic blood pressure and heart rate are measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal.

⁴ To include FEV₁, FEV₆, FVC, FEF₂₅₋₇₅, FEF₇₅, and PEFR.

⁵ Faecal occult blood is measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal. Baseline measure is taken from last FOB in Study 042 or Study 091.

⁶ Serum pregnancy test for female patients of child bearing potential. Urine test only is done at Follow-Up Visit.

⁷ A Diary Card is issued at each visit. The patient will use the Diary Card to record if they feel differently since the previous visit.

⁸ Patients will be assessed for GI AEs at every visit.



Protocol	Centre Number	Patient Number			
207499/040					

MODULE 4

Module 4: Visit 5 (Week 8) and Visit 6 (Week 12), Adverse Experiences, Conmeds, Medical Procedures, COPD Exacerbations, Resource Utilisation, Continuation/Withdrawal.

CRF Pages: 59 - 100

Unprocessed forms: Within this module the following occur which will generate attachments that need to be brought in-house.

Visit 6 :
St Georges Respiratory Questionnaire



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]	Visit Date Day Mth Yr [][][][][]	Visit 5 Week 8

PRESENTATION TO CLINIC

Record time of presentation to clinic [][][]
24hr:min

Note: Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.

Record the date and time of the patient's last dose of short-acting beta₂ agonist [][][][][][] 24hr:min
Day Mth Yr

Record the date and time of the patient's last dose of long-acting beta₂ agonist [][][][][][] 24hr:min
Day Mth Yr

Record the date and time of the patient's last dose of anticholinergic [][][][][][] 24hr:min
Day Mth Yr

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes → If 'Yes' please record time [][][]
24hr:min

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	[][][][][] Day Mth Yr	[][][][][] Day Mth Yr	[][][][][] Day Mth Yr	[][][][][] Day Mth Yr
Level of exacerbation (maximum intensity)	☐ Level 1	☐ Level 1	☐ Level 1	☐ Level 1
	☐ Level 2	☐ Level 2	☐ Level 2	☐ Level 2
	☐ Level 3	☐ Level 3	☐ Level 3	☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 5 Week 8

RESOURCE UTILISATION FOR COPD EXACERBATIONS

If the patient has received any COPD exacerbation related medical care since the previous visit, please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

*Review the diary card for illegible/incomplete entries **in the presence of the patient.***

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 5 Week 8

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)

Date and time of last dose of study medication prior to the study visit

Day Mth Yr

24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70					

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤ 120%?

- ☐ No → If 'No' please check the % compliance at the previous visit. If compliance was not ≥ 80% and ≤ 120% at the last visit, please withdraw the patient. Please complete the assessments for Visit 5 and the assessments for patients withdrawing or stopping the study at Visit 5, contained at the end of this visit.
- ☐ Yes



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 5 Week 8

SMOKING STATUS

Does the patient currently smoke ?

☐

No

☐

Yes



If 'Yes' please record the average number of cigarettes per day :

PULMONARY REHABILITATION PROGRAMME

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit ?

☐

No

☐

Yes

LABORATORY TESTS

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential). Please refer to the instructions on the SBCL shipping form and manual.

Blood Sample Date

Day
Mth
Yr

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below.

Attach label here

Are there any **clinically significant worsenings** since the previous visit ?

☐

No

☐

Yes



If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

Place the SBCL laboratory report in the plastic wallet at the back of this module.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 5 Week 8

URINALYSIS

Please perform urinalysis using the dipstick provided by SBCL and record the results in the patient notes.

Urine Sample Date

Day
Mth
Yr

Are the dipstick results negative?

- ☐ No —▶ If 'No' please send the sample to SBCL for microscopy
☐ Yes

Are there any **clinically significant worsenings** since the previous visit on the SBCL report?

- ☐ No
☐ Yes —▶ If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

PREGNANCY TEST

Is the patient a female of child-bearing potential ?

- ☐ No
☐ Yes —▶ If 'Yes' please request a pregnancy test on the SBCL requisition form.

Is the patient pregnant?

- ☐ No
☐ Yes —▶ If 'Yes' please withdraw the patient from the study, enter details in the Adverse Experience section. Complete the Early Withdrawal Visit (found as a separate book).



Protocol		Patient Number	Patient Initials		Visit 5 Week 8
207499/040					

OVERALL BREATHLESSNESS ASSESSMENT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 5 Week 8

INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)

Are there any **clinically significant worsenings** since the last visit ?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed:
Day Mth Yr

Were any clinically significant changes noted since the last visit ?

☐ No

☐ Yes → ☐ Improvement

☐ Worsening → *Enter details in the Adverse Experience section at the back of this module.*

Place the ECG trace in the plastic wallet at the back of this module.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 5 Week 8

PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and / or anticholinergic medications and / or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

STUDY MEDICATION LABEL

Issue the patient one bottle of open-label study medication (70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

**Attach study medication
label here**

Give the patient the first dose of study medication with food and record the date and time of administration below.

Date and time of administration
Day Mth Yr 24hr:min



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 5 Week 8

INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐ No —► If 'No' please complete the assessments for Visit 5 and the Assessments for Patients Withdrawing or Stopping the Study at Visit 5 contained on the following pages. Complete and fax the Withdrawal Form contained in the Withdrawal and Follow-Up Book.

☐ Yes —► If 'Yes' please;

- Issue a new diary card. Remind the patient to record if they feel differently since starting the study.
- Ask the patient to return for the next visit in 28 +/- 6 days.
- **Remind the patient:**
 - i to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.
 - ii **not** to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).
 - iii to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonists (long-acting) for **12 hours** before the next visit.
 - iv to refrain from smoking for **2 hours** immediately preceding the visit.
 - v to bring any remaining study medication or study medication containers and the diary card.
 - vi to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.



Protocol		Patient Number	Patient Initials		Visit 5 Week 8
207499/040					

ASSESSMENTS FOR PATIENTS WITHDRAWING OR STOPPING THE STUDY

Complete the assessments below only for patients who are withdrawing early from the study or stopping the study because the product has been registered or because the sponsor has terminated the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a clinically significant worsening in the patient's physical condition since the previous examination ?

☐

No

☐

Yes



If 'Yes' record details in the Adverse Experience section at the back of this module.



Protocol 207499/040		Patient Number [][][][][]	Patient Initials [][][][]		Visit 5 Week 8

FAECAL OCCULT BLOOD TEST

Issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-Up Visit.

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement : After 5 Minutes Supine

Blood Pressure mmHg systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure mmHg systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the previous assessment ?

☐

No

☐

Yes



If 'Yes' record details in the Adverse Experience section at the back of this module.

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Follow-Up Visit in 7 +/- 3 days.



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]	Visit Date Day Mth Yr [][][][][]	Visit 6 Week 12

PRESENTATION TO CLINIC

Record time of presentation to clinic [][][]
24hr:min

Note : Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.

Record the date and time of the patient's last dose of short-acting beta₂ agonist [][][][][] [][][]
Day Mth Yr 24hr:min

Record the date and time of the patient's last dose of long-acting beta₂ agonist [][][][][] [][][]
Day Mth Yr 24hr:min

Record the date and time of the patient's last dose of anticholinergic [][][][][] [][][]
Day Mth Yr 24hr:min

Has the patient smoked within the past 2 hours?

☐

No

☐

Yes



If 'Yes' please record time

[][][]
24hr:min

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 6 Week 12

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐

No

☐

Yes —▶ If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	Day Mth Yr	Day Mth Yr	Day Mth Yr	Day Mth Yr
Level of exacerbation (maximum intensity)	☐ Level 1	☐ Level 1	☐ Level 1	☐ Level 1
	☐ Level 2	☐ Level 2	☐ Level 2	☐ Level 2
	☐ Level 3	☐ Level 3	☐ Level 3	☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.



Protocol		Patient Number	Patient Initials		Visit 6 Week 12
207499/040					

RESOURCE UTILISATION FOR COPD EXACERBATIONS

Please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

Review the diary card for illegible/incomplete entries **in the presence of the patient**.

ADVERSE EXPERIENCES

Please complete the Adverse Experience section at the back of this module. If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

Please complete the Concomitant Medication section at the back of this module. If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.



Protocol 207499/040		Patient Number [][][][][][]	Patient Initials [][][][][]		Visit 6 Week 12

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)
[][][][][][]	[][][][][][]	[][]	
[][][][][][]	[][][][][][]	[][]	
[][][][][][]	[][][][][][]	[][]	

Date and time of last dose of study medication prior to the study visit

[][]	[][]	[][]	[][]	[][]	[][]
Day	Mth	Yr	24hr:	min	

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70	[][][]	[][][]	[][][]	[][][]	[][][][]

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤ 120%?

- ☐ No → If 'No' please check the % compliance at the previous visit. If compliance was not ≥ 80% and ≤ 120% at the last visit, please withdraw the patient. Please complete the assessments for Visit 6 and the assessments for patients withdrawing or stopping the study at Visit 6, contained at the end of this visit.
- ☐ Yes



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 6 Week 12

SMOKING STATUS

Does the patient currently smoke ?

☐

No

☐

Yes



If 'Yes' please record the average number of cigarettes per day :

PULMONARY REHABILITATION PROGRAMME

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit ?

☐

No

☐

Yes

LABORATORY TESTS

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential). Please refer to the instructions on the SBCL shipping form and manual.

Blood Sample Date

Day
Mth
Yr

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below.

Attach label here

Are there any **clinically significant worsenings** since the previous visit ?

☐

No

☐

Yes



If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

Place the SBCL laboratory report in the plastic wallet at the back of this module.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 6 Week 12

URINALYSIS

Please perform urinalysis using the dipstick provided by SBCL and record the results in the patient notes.

Urine Sample Date
Day Mth Yr

Are the dipstick results negative?

- ☐ No —▶ If 'No' please send the sample to SBCL for microscopy
☐ Yes

Are there any **clinically significant worsenings** since the previous visit on the SBCL report?

- ☐ No
☐ Yes —▶ If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

PREGNANCY TEST

Is the patient a female of child-bearing potential ?

- ☐ No
☐ Yes —▶ If 'Yes' please request a pregnancy test on the SBCL requisition form.

Is the patient pregnant?

- ☐ No
☐ Yes —▶ If 'Yes' please withdraw the patient from the study, enter details in the Adverse Experience section. Complete the Early Withdrawal Visit (found as a separate book).



Protocol 207499/040		Patient Number <table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>						Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						Visit 6 Week 12

OVERALL BREATHLESSNESS ASSESSMENT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 6 Week 12

INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)

Are there any **clinically significant worsenings** since the last visit ?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed:
Day Mth Yr

Were any clinically significant changes noted since the last visit ?

☐ No

☐ Yes → ☐ Improvement

☐ Worsening → *Enter details in the Adverse Experience section at the back of this module.*

Place the ECG trace in the plastic wallet at the back of this module.



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Protocol		Patient Number	Patient Initials		Visit 6 Week 12
207499/040					

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted ? *The distance walked should be entered even if the patient did not walk for 6 minutes. If the patient was too ill to attempt the test, please mark the 'Yes' box and enter 0 for distance walked.*

☐ No

☐ Yes → if 'Yes', Distance walked Metres

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

POST-EXERCISE BREATHLESSNESS (Immediately after the patient completes the exercise tolerance)
Heart Rate beats/min
Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

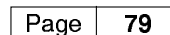
"How short of breath do you feel right now?"

Please rate your breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

- 0 Nothing at all
- 1 Very, very slight (just noticeable)
- 2 Very slight
- 3 Moderate
- 4 Somewhat severe
- 5 Severe
- 6
- 7 Very severe
- 8
- 9 Very, very severe (almost maximal)
- 10 Maximal

Post-exercise breathlessness score .
INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise tolerance test (rest for at least 10 minutes) before performing the pulmonary function tests.



Protocol		Patient Number	Patient Initials		Visit 6 Week 12
207499/040					

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and / or anticholinergic medications and / or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

Issue the patient one bottle of open-label study medication (70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

**Attach study medication
label here**

Give the patient the first dose of study medication with food and record the date and time of administration below.

Date and time of administration

Day	Mth	Yr	

24hr	min



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 6 Week 12

INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐ No —► If 'No' please complete the assessments for Visit 6 and the Assessments for Patients Withdrawing or Stopping the Study at Visit 6 contained on the following pages. Complete and fax the Withdrawal Form contained in the Withdrawal and Follow-Up Book.

☐ Yes —► If 'Yes' please;

- Issue a new diary card. Remind the patient to record if they feel differently since starting the study.
- Ask the patient to return for the next visit in 28 +/- 6 days.
- Complete the Study Continuation / Withdrawal page at the back of this module.
- **Remind the patient:**
 - i to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.
 - ii **not** to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).
 - iii to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonists (long-acting) for **12 hours** before the next visit.
 - iv to refrain from smoking for **2 hours** immediately preceding the visit.
 - v to bring any remaining study medication or study medication containers and the diary card.
 - vi to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 6 Week 12

ASSESSMENTS FOR PATIENTS WITHDRAWING OR STOPPING THE STUDY

Complete the assessments below only for patients who are withdrawing early from the study or stopping the study because the product has been registered or because the sponsor has terminated the study.

SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a clinically significant worsening in the patient's physical condition since the previous examination ?

☐

No

☐

Yes

→ If 'Yes' record details in the Adverse Experience section at the back of this module.



Protocol 207499/040		Patient Number [][][][][]	Patient Initials [][][][]		Visit 6 Week 12

FAECAL OCCULT BLOOD TEST

Issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-up Visit.

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement : After 5 Minutes Supine

Blood Pressure mmHg systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure mmHg systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the previous assessment ?

☐

No

☐

Yes



If 'Yes' record details in the Adverse Experience section at the back of this module.

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Follow-Up Visit in 7 +/- 3 days.

ADVERSE EXPERIENCES (Non-serious)**DEFINITIONS****INTENSITY (Maximum)**

MILD	<i>Adverse experience which is easily tolerated</i>
MODERATE	<i>Adverse experience sufficiently discomforting to interfere with daily activity</i>
SEVERE	<i>Adverse experience which prevents normal everyday activities</i>

RELATIONSHIP TO INVESTIGATIONAL DRUG

NOT RELATED	<i>The adverse experience is definitely not related to the test drug</i>
UNLIKELY	<i>There are other more likely causes and the drug is not suspected as a cause</i>
SUSPECTED (REASONABLE POSSIBILITY)	<i>A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug</i>
PROBABLE	<i>There probably is a direct cause and effect relationship between the adverse experience and the study drug</i>

SERIOUS ADVERSE EXPERIENCE (SAE)

A SAE is any experience which is :-

- 1 - fatal
- 2 - life threatening
- 3 - disabling/incapacitating
- 4 - results in hospitalisation (excluding elective surgery or routine clinical procedures)
- 5 - prolongs a hospital stay
- 6 - associated with congenital abnormality
- 7 - cancer
- 8 - associated with overdose
- 9 - In addition any event which the investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug should be reported as a serious event

IF A SAE OCCURS, PLEASE GO TO THE SAE SECTION IMMEDIATELY AND FOLLOW THE INSTRUCTIONS GIVEN THERE

Use each form for a maximum of two experiences

PLEASE REMEMBER ALL QUESTIONS ON ADVERSE EXPERIENCES FORM SHOULD BE COMPLETED



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Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Do you feel different in any way since starting the treatment or since the previous module?" Provide the diagnosis **not** symptoms where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbation section.

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the SAE section (See opposite for definitions of an SAE).

If no adverse experiences occurred since the previous module, please sign form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Mth Yr 24hr:min	 Day Mth Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Mth Yr 24hr:min	 Day Mth Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy <i>If 'Yes', record details in the Concomitant Medication and / or Medical Procedures section</i> ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Mth Yr	



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Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Do you feel different in any way since starting the treatment or since the previous module?" Provide the diagnosis **not** symptoms where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbation section.

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the SAE section (See opposite for definitions of an SAE).

If no further adverse experiences or changes in adverse experiences occurred since the previous module, please sign form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
End Date and Time (If ongoing please leave blank)	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
Outcome If patient died, STOP: go to SAE section and follow instructions given there ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures section ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE ?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Mth Yr	



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Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Do you feel different in any way since starting the treatment or since the previous module?" Provide the diagnosis **not** symptoms where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbation section.

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the SAE section (See opposite for definitions of an SAE).

If no further adverse experiences or changes in adverse experiences occurred since the previous module, please sign form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
End Date and Time (If ongoing please leave blank)	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
Outcome If patient died, STOP: go to SAE section and follow instructions given there ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures section ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE ?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Mth Yr	



Protocol	Centre Number	Patient Number	Patient Initials		
207499/040					

CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the previous module.
(Please write using BLOCK CAPITALS)

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

☐ No concomitant medication changes since the previous module

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experience section using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the start and end date.

Drug Name (Trade name preferred)	Unit Dose (e.g. 500mg)	Frequency (e.g. bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of a diagnosis)	Start Date (be as precise as possible) Day Mth Yr	End Date (or if continuing mark box) Day Mth Yr	
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							

* For Route, see tab for acceptable abbreviations.



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][]		

CONCOMITANT MEDICATION - Continued

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experience section using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the start and end date.

Drug Name (Trade name preferred)	Unit Dose (e.g. 500mg)	Frequency (e.g. bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of a diagnosis)	Start Date (be as precise as possible)			End Date (or if continuing mark box)		
					Day	Mth	Yr	Day	Mth	Yr
					[][][]	[][][]	[][][]	[][][]	[][][]	[]
For SB										
					[][][]	[][][]	[][][]	[][][]	[][][]	[]
For SB										
					[][][]	[][][]	[][][]	[][][]	[][][]	[]
For SB										
					[][][]	[][][]	[][][]	[][][]	[][][]	[]
For SB										
					[][][]	[][][]	[][][]	[][][]	[][][]	[]
For SB										
					[][][]	[][][]	[][][]	[][][]	[][][]	[]
For SB										
					[][][]	[][][]	[][][]	[][][]	[][][]	[]
For SB										
					[][][]	[][][]	[][][]	[][][]	[][][]	[]
For SB										

* For Route, see tab for acceptable abbreviations.



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][][]	Patient Initials [][][][]	Visit Date Day Mth Yr [][][][][]	

MEDICAL PROCEDURES (Excluding treatment for COPD exacerbations)

Do not record procedures used to treat COPD exacerbations here, record them in the COPD Exacerbations section.

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed since the previous module ?

☐ No

☐ Yes —▶ If 'Yes', please record details below using standard medical terminology

All indications for procedures should be recorded in the Adverse Experience section.

Procedure	Indication	Procedure Start Date			Procedure End Date		
		Day	Mth	Yr	Day	Mth	Yr
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							



Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy. All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages.**

If no COPD Exacerbations since the previous module, please sign form below and mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
End Date and Time (If ongoing please leave blank)	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
Outcome If patient died, STOP: go to SAE COPD Exacerbation pages	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent ☐ Constant	☐ Intermittent ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures section	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE ?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Mth Yr	



Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy. All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages.**

If no further COPD Exacerbations or changes to COPD Exacerbations have occurred since the previous study, please sign form below and mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
End Date and Time (If ongoing please leave blank)	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
Outcome If patient died, STOP: go to SAE COPD Exacerbation pages	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent ☐ Constant	☐ Intermittent ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures section	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE ?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Mth Yr	



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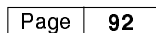
Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy. All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages.**

If no further COPD Exacerbations or changes to COPD Exacerbations have occurred since the previous study, please sign form below and mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	 Day Mth Yr 24hr:min	 Day Mth Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Mth Yr 24hr:min	 Day Mth Yr 24hr:min
Outcome If patient died, STOP: go to SAE COPD Exacerbation pages	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent ☐ Constant	☐ Intermittent ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures section	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE ?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____		Date : Day Mth Yr



Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date
207499/040				
				Day Mth Yr

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience	COPD Exacerbation	➤ Specify reason(s) for considering this a serious AE. Mark all that apply. 1 2 3 4 5 6 7 8 9 ☐ fatal ☐ life threatening ☐ disabling/incapacitating ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) ☐ hospitalisation prolonged ☐ congenital abnormality ☐ cancer ☐ overdose ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	Day Mth Yr 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	Day Mth Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent ➤ No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate ? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased) ☐ Yes ☐ No If yes, did SAE recur ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	➤ Assessment The SAE is probably associated with : ☐ Protocol design or procedures (but not to study drug) <i>Please specify</i> _____ ☐ Another condition (eg, condition under study, intercurrent illness) <i>Please specify</i> _____ ☐ Another drug <i>Please specify</i> _____
Corrective Therapy <i>If 'Yes', record details in the COPD Medication or Procedures pages</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)

Relevant Laboratory Data

Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

If applicable, was randomisation code broken at investigational site ? ☐ No ☐ Yes

Randomisation / Study Medication Number : [][][][][]

Investigator's Signature : _____
(confirming that the above data are accurate and complete)

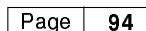
Date [][][][][]
Day Mth Yr

Please PRINT name _____

SB Medical Monitor's Signature : _____

Date [][][][][]
Day Mth Yr

Please PRINT name _____



Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date
207499/040				
				Day Mth Yr

Person Reporting SAE _____ (Please print clearly)		AEGIS Number _____	
Serious Adverse Experience	COPD Exacerbation	➤ Specify reason(s) for considering this a serious AE. Mark all that apply.	
For SmithKline Beecham			
Onset Date and Time	Day Mth Yr 24hr:min		
End Date and Time (If ongoing please leave blank)	Day Mth Yr 24hr:min		
Outcome If patient died, please complete Form D	☐ Resolved ☐ Ongoing ☐ Died	1 ☐ fatal 2 ☐ life threatening 3 ☐ disabling/incapacitating 4 ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) 5 ☐ hospitalisation prolonged 6 ☐ congenital abnormality 7 ☐ cancer 8 ☐ overdose 9 ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution	
Experience Course	☐ Intermittent ➤ No. of episodes ☐ Constant		
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe		
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate ? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased) ☐ Yes ☐ No If yes, did SAE recur ☐ Yes ☐ No	
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	➤ Assessment The SAE is probably associated with : ☐ Protocol design or procedures (but not to study drug) Please specify _____ ☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____ ☐ Another drug Please specify _____	
Corrective Therapy If 'Yes', record details in the COPD Medication or Procedures pages	☐ Yes ☐ No		
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No		



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)

Relevant Laboratory Data

Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

If applicable, was randomisation code broken at investigational site ? ☐ No ☐ Yes

Randomisation / Study Medication Number : [][][][][]

Investigator's Signature : _____ **Date**

Day Mth Yr

(confirming that the above data are accurate and complete)

Please PRINT name _____

SB Medical Monitor's Signature : _____ **Date**

Day Mth Yr

Please PRINT name _____

Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]		

MEDICATION FOR COPD EXACERBATIONS

Has the patient taken any medication for COPD exacerbations since the previous module ?

☐

No

☐

Yes → If 'Yes', please record details below

Drug Name (Trade name preferred)	Unit Dose (e.g. 500mg)	Frequency (e.g. bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of a diagnosis)	Start Date (be as precise as possible) Day Mth Yr	End Date (or if continuing mark box) Day Mth Yr	
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							

* For Route, see General Instructions for acceptable abbreviations.



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]		

MEDICAL PROCEDURES FOR COPD EXACERBATIONS

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since the previous module ?

☐ No

☐ Yes —▶ If 'Yes', please record details below using standard medical terminology

Procedure	Indication	Procedure Start Date			Procedure End Date		
		Day	Mth	Yr	Day	Mth	Yr
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							



Protocol 207499/040	Centre Number [][][][][]	Patient Number [][][][][][][]	Patient Initials [][][][][]		

HEALTHCARE RESOURCE UTILISATION FOR COPD EXACERBATIONS

Complete this form for any **COPD exacerbation related medical care** the patient received since the previous module

Physician Visits (i.e., COPD care excluding scheduled protocol visits)

☐ There were no physician visits since the previous module

Date of Visit			Reason for Visit
Day	Mth	Yr	
[][][][][]			
[][][][][]			
[][][][][]			
[][][][][]			
[][][][][]			
[][][][][]			
[][][][][]			
[][][][][]			

Emergency Room (ER)/Urgent Care Visits/Casualty Department Procedures (i.e., lung surgery)

☐ There were no Emergency Room/Urgent Care Visits/Casualty Department Procedures since previous module

Date of Visit			Reason for Visit		Patient Admitted from ER ?	
					Yes	No
Day	Mth	Yr				
[][][][][]					☐	☐
[][][][][]					☐	☐
[][][][][]					☐	☐
[][][][][]					☐	☐
[][][][][]					☐	☐
[][][][][]					☐	☐
[][][][][]					☐	☐

Protocol	Centre Number	Patient Number	Patient Initials		
207499/040					

HEALTHCARE RESOURCE UTILISATION FOR COPD EXACERBATIONS - continued

Hospitalisations (also record details of any hospitalisations in the Serious Adverse Experience - COPD Exacerbation section)

☐ There were no hospitalisations since the previous module

Date of Admission			Date of Discharge			Reason for Admission
Day	Mth	Yr	Day	Mth	Yr	

Intensive Care Unit (ICU) stays (did the patient stay in the ICU during any of the above hospitalisations?)

☐ There were no ICU stays since the previous module

Date Admitted to ICU			Date Discharged from ICU			Reason for ICU Admission
Day	Mth	Yr	Day	Mth	Yr	

Lost Work Days (i.e., days patient missed work due to COPD excluding scheduled protocol visits)

☐ There were no lost work days since the previous module

Start Date			Stop Date			Reason for Absence
Day	Mth	Yr	Day	Mth	Yr	



Protocol	Centre Number	Patient Number	Patient Initials		
207499/040					

STUDY CONTINUATION / WITHDRAWAL

Is the patient continuing in the study ?

☐ Yes

☐ No → If 'No' please mark the **PRIMARY** cause of withdrawal and enter the date of the final visit and the date of the final dose.

1	☐ Adverse experience (complete AE form)
2	☐ Insufficient therapeutic effect
3	☐ Protocol deviation (including non-compliance)
4	☐ Lost to follow-up
5	☐ Other - specify:

Date of Final Visit

Day	Mth	Yr

Date of Final Dose

Day	Mth	Yr

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data on this case report form and that all information is complete and accurate.

Investigator's Signature Date

Day	Mth	Yr

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)

SAEs MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS

COMPLETE THE SAE PAGES OPPOSITE

Please complete these pages as fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Experience Course' blank and update it later

SIGN AND DATE THE SAE PAGE**PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE**

- Demography
- Significant Medical/Surgical History and Physical Examination
- Study Medication Record
- Concomitant Medication
- Form D (if applicable)

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE

(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO :

Your local SB CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local SB CRA/Medical monitor within 24 hours



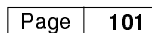
Protocol	Centre Number	Patient Number										
207499/040	<table border="1"><tr><td></td><td></td><td></td></tr></table>				<table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>							

MOD5 & MOD6 - SERIOUS ADVERSE EXPERIENCES

MOD5 & 6: **Serious Adverse Experiences**

MOD5 : 101, 102

MOD6 : 103, 104



Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date
207499/040				Day Mth Yr

Person Reporting SAE _____ (Please print clearly)		AEGIS Number . 	
Serious Adverse Experience (Please print clearly)		➔ Specify reason(s) for considering this a serious AE. Mark all that apply.	
For SmithKline Beecham		1 ☐ fatal 2 ☐ life threatening 3 ☐ disabling/incapacitating 4 ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) 5 ☐ hospitalisation prolonged 6 ☐ congenital abnormality 7 ☐ cancer 8 ☐ overdose 9 ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution	
Onset Date and Time	Day Mth Yr 24hr:min		
End Date and Time (If ongoing please leave blank)	Day Mth Yr 24hr:min		
Outcome If patient died, please complete Form D	☐ Resolved ☐ Ongoing ☐ Died		
Experience Course	☐ Intermittent ➔ No. of episodes ☐ Constant		
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe		
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped		
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable		
Corrective Therapy If 'Yes', record details in the Concomitant Medication section	☐ Yes ☐ No		
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No		
		Did the SAE abate ? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased) ☐ Yes ☐ No If yes, did SAE recur ☐ Yes ☐ No	
		Assessment The SAE is probably associated with : ☐ Protocol design or procedures (but not to study drug) Please specify _____ ☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____ ☐ Another drug Please specify _____	

Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 	

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data**

Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	 Day Mth Yr			
	 Day Mth Yr			
	 Day Mth Yr			
	 Day Mth Yr			

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

If applicable, was randomisation code broken at investigational site ? ☐ No ☐ Yes

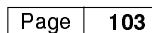
Randomisation / Study Medication Number :

Investigator's Signature : _____ **Date**
 Day Mth Yr
 (confirming that the above data are accurate and complete)

Please PRINT name _____

SB Medical Monitor's Signature : _____ **Date**
 Day Mth Yr

Please PRINT name _____



Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date
207499/040				
				Day Mth Yr

Person Reporting SAE _____ <i>(Please print clearly)</i>						AEGIS Number	[][][][][][][][][][][] . [][]
Serious Adverse Experience <i>(Please print clearly)</i>						➤ Specify reason(s) for considering this a serious AE. Mark all that apply.	
For SmithKline Beecham							
Onset Date and Time	[][]	[][]	[][]	[][]	[][]		
	Day	Mth	Yr	24hr:	min		
End Date and Time <i>(If ongoing please leave blank)</i>	[][]	[][]	[][]	[][]	[][]		
	Day	Mth	Yr	24hr:	min		
Outcome If patient died, please complete Form D ←	☐ Resolved ☐ Ongoing ☐ Died						
Experience Course	☐ Intermittent ➤ No. of episodes ☐ Constant						
Intensity (<i>maximum</i>)	☐ Mild ☐ Moderate ☐ Severe						
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped					Did the SAE abate ? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased) ☐ Yes ☐ No If yes, did SAE recur ☐ Yes ☐ No	
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable					➤ Assessment The SAE is probably associated with : ☐ Protocol design or procedures (but not to study drug) <i>Please specify</i> _____ ☐ Another condition (eg, condition under study, intercurrent illness) <i>Please specify</i> _____ ☐ Another drug <i>Please specify</i> _____	
Corrective Therapy If 'Yes', record details in the Concomitant Medication section ←	☐ Yes ☐ No						
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No						

Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 	

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data**

Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	 Day Mth Yr			
	 Day Mth Yr			
	 Day Mth Yr			
	 Day Mth Yr			

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

If applicable, was randomisation code broken at investigational site ? ☐ No ☐ Yes

Randomisation / Study Medication Number :

Investigator's Signature : _____ **Date**
 Day Mth Yr
 (confirming that the above data are accurate and complete)

Please PRINT name _____

SB Medical Monitor's Signature : _____ **Date**
 Day Mth Yr

Please PRINT name _____

Protocol	Centre Number	Patient Number	Patient Initials
207499/040			

CONFIDENTIAL

**PROTOCOL SB 207499/040****BOOK 3 : VISITS 7 AND 8 (WEEKS 16 AND 20)**

**A MULTICENTRE, OPEN-LABEL EXTENSION STUDY
TO EVALUATE THE SAFETY, TOLERABILITY AND EFFICACY
OF ORAL SB 207499 (15mg TWICE DAILY) IN PATIENTS WITH
CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)**

GENERAL INSTRUCTIONS

- Write clearly in capital letters using a black ball point pen and press firmly so that all copies are legible
- Do not write in shaded areas
- Answer ALL questions on every page
- Enter "N/A" if information requested is not available
- Initial and date all changes, additions or deletions. Use a single pen stroke to remove an incorrect entry
- Enter the patient initials on all pages on which information has been entered and the patient number and centre number where required
- Do not enter additional data/information after the set of CRF pages has been split/separated
- The cover flap or plastic writing board should be used to divide each set of pages before writing on them with a ball point pen

DATE

Please use the following three-letter abbreviations for the months :

January	JAN
February	FEB
March	MAR
April	APR
May	MAY
June	JUN
July	JUL
August	AUG
September	SEP
October	OCT
November	NOV
December	DEC

e.g.

0	1	J	A	N	9	9
Day		Mth			Yr	

 = 1st January 1999

TIME

Unless specified otherwise, please use the 24 hour clock :

e.g.

1	5	3	0
24hr:min			

 = 3.30 p.m.

PATIENT INITIALS

Please use the following format ;

e.g. XXXXXXXXXX

ROUTE KEY FOR PRIOR/CONCOMITANT MEDICATION PAGE

PO = By mouth	SL = Sublingual	TD = Transdermal
IV = Intravenous	IT = Intrathecal	IH = Inhaled
IM = Intramuscular	VA = Vaginal	SC = Subcutaneous
IAR = Intra-arterial	NA = Nasal	PR = Rectal
TO = Topical	IA = Intra-articular injection	ID = Intradermal

SUMMARY CHART OF STUDY PROCEDURES (OPEN BOXES)
PROTOCOL SB 207499/040

Mark open boxes to confirm that each procedure has been completed.

Procedures	Visit 7	Visit 8
	Week 16	Week 20
Signed written informed consent		
Study Medication compliance		
Concomitant Medication		
Diary Card Review ⁷		
Adverse Experiences ⁸		
COPD Exacerbation assessment/Healthcare Ut.		
Physical (Including Respiratory) Examination		
Resting 12-Lead ECG		
Vital Signs (BP, HR) ³		
Overall Breathlessness (Modified Borg)		
Exercise Tolerance Test - 6 Minute Walk		
Post Exercise Breathlessness		
Pulmonary Function Tests ⁴		
Laboratory Tests ⁵		
Pregnancy Test ⁶		
Quality of Life Assessment: SGRQ		
Quality of Life Assessment: SF-36		
Dispense or re-dispense Open-Label Medication		
Study Continuation / Withdrawal		

³ Orthostatic blood pressure and heart rate are measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal.

⁴ To include FEV₁, FEV₆, FVC, FEF₂₅₋₇₅, FEF₇₅, and PEFR.

⁵ Faecal occult blood is measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal. Baseline measure is taken from last FOB in Study 042 or Study 091.

⁶ Serum pregnancy test for female patients of child bearing potential. Urine test only is done at Follow-Up Visit.

⁷ A Diary Card is issued at each visit. The patient will use the Diary Card to record if they feel differently since the previous visit.

⁸ Patients will be assessed for GI AEs at every visit.



Protocol	Centre Number	Patient Number			
207499/040					

MODULE 7

Module 7: Visit 7 (Week 16) and Visit 8 (Week 20), Adverse Experiences, Conmeds, Medical Procedures, COPD Exacerbations, Resource Utilisation, Continuation/Withdrawal.

CRF Pages: 105 - 144

Unprocessed forms: Within this module the following occur which will generate attachments that need to be brought in-house.

None



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Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]	Visit Date Day Mth Yr [][][][][]	Visit 7 Week 16

PRESENTATION TO CLINIC

Record time of presentation to clinic [][][]
24hr:min

Note: Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.

Record the date and time of the patient's last dose of short-acting beta₂ agonist [][][][][][] 24hr:min
Day Mth Yr

Record the date and time of the patient's last dose of long-acting beta₂ agonist [][][][][][] 24hr:min
Day Mth Yr

Record the date and time of the patient's last dose of anticholinergic [][][][][][] 24hr:min
Day Mth Yr

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes → If 'Yes' please record time [][][] 24hr:min

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	[][][][][][] Day Mth Yr	[][][][][][] Day Mth Yr	[][][][][][] Day Mth Yr	[][][][][][] Day Mth Yr
Level of exacerbation (maximum intensity)	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 7 Week 16

RESOURCE UTILISATION FOR COPD EXACERBATIONS

If the patient has received any COPD exacerbation related medical care since the previous visit, please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

*Review the diary card for illegible/incomplete entries **in the presence of the patient.***

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.



Protocol 207499/040		Patient Number [][][][][][]	Patient Initials [][][][][]		Visit 7 Week 16

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)
[][][][][][]	[][][][][][]	[]	
[][][][][][]	[][][][][][]	[]	
[][][][][][]	[][][][][][]	[]	

Date and time of last dose of study medication prior to the study visit

[][]	[][]	[][]	[][]	[][]	[][]
Day	Mth	Yr	24hr:	min	

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70	[][]	[][]	[][]	[][]	[][][][]

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤ 120%?

- ☐ No → If 'No' please check the % compliance at the previous visit. If compliance was not ≥ 80% and ≤ 120% at the last visit, please withdraw the patient. Please complete the assessments for Visit 7 and the assessments for patients withdrawing or stopping the study at Visit 7, contained at the end of this visit.
- ☐ Yes



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 7 Week 16

SMOKING STATUS

Does the patient currently smoke ?

☐

No

☐

Yes



If 'Yes' please record the average number of cigarettes per day :

PULMONARY REHABILITATION PROGRAMME

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit ?

☐

No

☐

Yes

LABORATORY TESTS

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential). Please refer to the instructions on the SBCL shipping form and manual.

Blood Sample Date

Day
Mth
Yr

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below.

Attach label here

Are there any **clinically significant worsenings** since the previous visit ?

☐

No

☐

Yes



If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

Place the SBCL laboratory report in the plastic wallet at the back of this module.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 7 Week 16

URINALYSIS

Please perform urinalysis using the dipstick provided by SBCL and record the results in the patient notes.

Urine Sample Date
Day Mth Yr

Are the dipstick results negative?

- ☐ No —▶ If 'No' please send the sample to SBCL for microscopy
☐ Yes

Are there any **clinically significant worsenings** since the last visit on the SBCL report?

- ☐ No
☐ Yes —▶ If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

PREGNANCY TEST

Is the patient a female of child-bearing potential ?

- ☐ No
☐ Yes —▶ If 'Yes' please request a pregnancy test on the SBCL requisition form.

Is the patient pregnant?

- ☐ No
☐ Yes —▶ If 'Yes' please withdraw the patient from the study, enter details in the Adverse Experience section. Complete the Early Withdrawal Visit (found as a separate book).



Protocol 207499/040		Patient Number <table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>						Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						Visit 7 Week 16

OVERALL BREATHLESSNESS ASSESSMENT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 7 Week 16

INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)

Are there any **clinically significant worsenings** since the last visit ?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed:
Day Mth Yr

Were any clinically significant changes noted since the last visit ?

☐ No

☐ Yes → ☐ Improvement

☐ Worsening → *Enter details in the Adverse Experience section at the back of this module.*

Place the ECG trace in the plastic wallet at the back of this module.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 7 Week 16

PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and / or anticholinergic medications and / or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

STUDY MEDICATION LABEL

Issue the patient one bottle of open-label study medication (70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

Attach study medication
label here

Give the patient the first dose of study medication with food and record the date and time of administration below.

Date and time of administration
Day Mth Yr 24hr:min



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 7 Week 16

INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐ No —► If 'No' please complete the assessments for Visit 7 and the Assessments for Patients Withdrawing or Stopping the Study at Visit 7 contained on the following pages. Complete and fax the Withdrawal Form contained in the Withdrawal and Follow-Up Book.

☐ Yes —► If 'Yes' please;

- Issue a new diary card. Remind the patient to record if they feel differently since starting the study.
- Ask the patient to return for the next visit in 28 +/- 6 days.
- **Remind the patient:**
 - i to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.
 - ii **not** to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).
 - iii to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonists (long-acting) for **12 hours** before the next visit.
 - iv to refrain from smoking for **2 hours** immediately preceding the visit.
 - v to bring any remaining study medication or study medication containers and the diary card.
 - vi to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 7 Week 16

ASSESSMENTS FOR PATIENTS WITHDRAWING OR STOPPING THE STUDY

Complete the assessments below only for patients who are withdrawing early from the study or stopping the study because the product has been registered or because the sponsor has terminated the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a clinically significant worsening in the patient's physical condition since the previous examination ?

☐

No

☐

Yes



If 'Yes' record details in the Adverse Experience section at the back of this module.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 7 Week 16

FAECAL OCCULT BLOOD TEST

Issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-Up Visit.

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement : After 5 Minutes Supine

Blood Pressure mmHg systolic / diastolic	Heart Rate beats/min

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure mmHg systolic / diastolic	Heart Rate beats/min

Are there any **clinically significant worsenings** since the previous assessment ?

☐

No

☐

Yes



If 'Yes' record details in the Adverse Experience section at the back of this module.

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Follow-Up Visit in 7 +/- 3 days.



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Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]	Visit Date Day Mth Yr [][][][][]	Visit 8 Week 20

PRESENTATION TO CLINIC

Record time of presentation to clinic [][][]
24hr:min

Note: Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.

Record the date and time of the patient's last dose of short-acting beta₂ agonist [][][][][][] 24hr:min
Day Mth Yr

Record the date and time of the patient's last dose of long-acting beta₂ agonist [][][][][][] 24hr:min
Day Mth Yr

Record the date and time of the patient's last dose of anticholinergic [][][][][][] 24hr:min
Day Mth Yr

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes → If 'Yes' please record time [][][] 24hr:min

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	[][][][][][] Day Mth Yr	[][][][][][] Day Mth Yr	[][][][][][] Day Mth Yr	[][][][][][] Day Mth Yr
Level of exacerbation (maximum intensity)	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 8 Week 20

RESOURCE UTILISATION FOR COPD EXACERBATIONS

Please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

Review the diary card for illegible/incomplete entries **in the presence of the patient**.

ADVERSE EXPERIENCES

Please complete the Adverse Experience section at the back of this module. If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

Please complete the Concomitant Medication section at the back of this module. If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 8 Week 20

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)

Date and time of last dose of study medication prior to the study visit

Day Mth Yr

24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70					

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤ 120%?

- ☐ No → If 'No' please check the % compliance at the previous visit. If compliance was not ≥ 80% and ≤ 120% at the last visit, please withdraw the patient. Please complete the assessments for Visit 8 and the assessments for patients withdrawing or stopping the study at Visit 8, contained at the end of this visit.
- ☐ Yes



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 8 Week 20

SMOKING STATUS

Does the patient currently smoke ?

☐

No

☐

Yes



If 'Yes' please record the average number of cigarettes per day :

PULMONARY REHABILITATION PROGRAMME

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit ?

☐

No

☐

Yes

LABORATORY TESTS

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential). Please refer to the instructions on the SBCL shipping form and manual.

Blood Sample Date

Day
Mth
Yr

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below.

Attach label here

Are there any **clinically significant worsenings** since the previous visit ?

☐

No

☐

Yes



If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

Place the SBCL laboratory report in the plastic wallet at the back of this module.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 8 Week 20

URINALYSIS

Please perform urinalysis using the dipstick provided by SBCL and record the results in the patient notes.

Urine Sample Date
Day Mth Yr

Are the dipstick results negative?

- ☐ No —▶ If 'No' please send the sample to SBCL for microscopy
☐ Yes

Are there any **clinically significant worsenings** since the previous visit on the SBCL report?

- ☐ No
☐ Yes —▶ If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

PREGNANCY TEST

Is the patient a female of child-bearing potential ?

- ☐ No
☐ Yes —▶ If 'Yes' please request a pregnancy test on the SBCL requisition form.

Is the patient pregnant?

- ☐ No
☐ Yes —▶ If 'Yes' please withdraw the patient from the study, enter details in the Adverse Experience section. Complete the Early Withdrawal Visit (found as a separate book).



Protocol		Patient Number	Patient Initials		Visit 8 Week 20									
207499/040		<table><tr><td></td><td></td><td></td><td></td><td></td></tr></table>						<table><tr><td></td><td></td><td></td><td></td></tr></table>						

OVERALL BREATHLESSNESS ASSESSMENT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 8 Week 20

INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)

Are there any **clinically significant worsenings** since the last visit ?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed:
Day Mth Yr

Were any clinically significant changes noted since the last visit ?

☐ No

☐ Yes → ☐ Improvement

☐ Worsening → *Enter details in the Adverse Experience section at the back of this module.*

Place the ECG trace in the plastic wallet at the back of this module.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 8 Week 20

PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and / or anticholinergic medications and / or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

STUDY MEDICATION LABEL

Issue the patient one bottle of open-label study medication (70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

Attach study medication
label here

Give the patient the first dose of study medication with food and record the date and time of administration below.

Date and time of administration
Day Mth Yr 24hr:min



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 8 Week 20

INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐ No —► If 'No' please complete the assessments for Visit 8 and the Assessments for Patients Withdrawing or Stopping the Study at Visit 8 contained on the following pages. Complete and fax the Withdrawal Form contained in the Withdrawal and Follow-Up Book.

☐ Yes —► If 'Yes' please;

- Issue a new diary card. Remind the patient to record if they feel differently since starting the study.
- Ask the patient to return for the next visit in 28 +/- 6 days.
- Complete the Study Continuation / Withdrawal page at the back of this module.
- **Remind the patient:**
 - i to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.
 - ii **not** to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).
 - iii to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonists (long-acting) for **12 hours** before the next visit.
 - iv to refrain from smoking for **2 hours** immediately preceding the visit.
 - v to bring any remaining study medication or study medication containers and the diary card.
 - vi to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 8 Week 20

ASSESSMENTS FOR PATIENTS WITHDRAWING OR STOPPING THE STUDY

Complete the assessments below only for patients who are withdrawing early from the study or stopping the study because the product has been registered or because the sponsor has terminated the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a clinically significant worsening in the patient's physical condition since the previous examination ?

☐

No

☐

Yes



If 'Yes' record details in the Adverse Experience section at the back of this module.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 8 Week 20

FAECAL OCCULT BLOOD TEST

Issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-Up Visit.

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement : After 5 Minutes Supine

Blood Pressure mmHg systolic / diastolic	Heart Rate beats/min
/	

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure mmHg systolic / diastolic	Heart Rate beats/min
/	

Are there any **clinically significant worsenings** since the previous assessment ?

☐

No

☐

Yes



If 'Yes' record details in the Adverse Experience section at the back of this module.

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Follow-Up Visit in 7 +/- 3 days.

ADVERSE EXPERIENCES (Non-serious)**DEFINITIONS****INTENSITY (Maximum)**

MILD	<i>Adverse experience which is easily tolerated</i>
MODERATE	<i>Adverse experience sufficiently discomforting to interfere with daily activity</i>
SEVERE	<i>Adverse experience which prevents normal everyday activities</i>

RELATIONSHIP TO INVESTIGATIONAL DRUG

NOT RELATED	<i>The adverse experience is definitely not related to the test drug</i>
UNLIKELY	<i>There are other more likely causes and the drug is not suspected as a cause</i>
SUSPECTED (REASONABLE POSSIBILITY)	<i>A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug</i>
PROBABLE	<i>There probably is a direct cause and effect relationship between the adverse experience and the study drug</i>

SERIOUS ADVERSE EXPERIENCE (SAE)

A SAE is any experience which is :-

- 1 - fatal
- 2 - life threatening
- 3 - disabling/incapacitating
- 4 - results in hospitalisation (excluding elective surgery or routine clinical procedures)
- 5 - prolongs a hospital stay
- 6 - associated with congenital abnormality
- 7 - cancer
- 8 - associated with overdose
- 9 - In addition any event which the investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug should be reported as a serious event

IF A SAE OCCURS, PLEASE GO TO THE SAE SECTION IMMEDIATELY AND FOLLOW THE INSTRUCTIONS GIVEN THERE

Use each form for a maximum of two experiences

PLEASE REMEMBER ALL QUESTIONS ON ADVERSE EXPERIENCES FORM SHOULD BE COMPLETED



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Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Do you feel different in any way since starting the treatment or since the previous module?" Provide the diagnosis **not** symptoms where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbation section.

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the SAE section (See opposite for definitions of an SAE).

If no adverse experiences occurred since the previous module, please sign form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Mth Yr 24hr:min	 Day Mth Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Mth Yr 24hr:min	 Day Mth Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy <i>If 'Yes', record details in the Concomitant Medication and / or Medical Procedures section</i> ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Mth Yr	



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Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Do you feel different in any way since starting the treatment or since the previous module?" Provide the diagnosis **not** symptoms where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbation section.

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the SAE section (See opposite for definitions of an SAE).

If no further adverse experiences or changes in adverse experiences occurred since the previous module, please sign form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
End Date and Time (If ongoing please leave blank)	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
Outcome If patient died, STOP: go to SAE section and follow instructions given there ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures section ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE ?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Mth Yr	



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Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Do you feel different in any way since starting the treatment or since the previous module?" Provide the diagnosis **not** symptoms where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbation section.

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the SAE section (See opposite for definitions of an SAE).

If no further adverse experiences or changes in adverse experiences occurred since the previous module, please sign form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
End Date and Time (If ongoing please leave blank)	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
Outcome If patient died, STOP: go to SAE section and follow instructions given there ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures section ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE ?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Mth Yr	



Protocol	Centre Number	Patient Number	Patient Initials		
207499/040					

CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the previous module.
(Please write using BLOCK CAPITALS)

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

☐ No concomitant medication changes since the previous module

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experience section using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the start and end date.

Drug Name (Trade name preferred)	Unit Dose (e.g. 500mg)	Frequency (e.g. bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of a diagnosis)	Start Date (be as precise as possible) Day Mth Yr	End Date (or if continuing mark box) Day Mth Yr	
							☐
For SB							
							☐
For SB							
							☐
For SB							
							☐
For SB							
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							☐
For SB							
							☐
For SB							

* For Route, see tab for acceptable abbreviations.



Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

CONCOMITANT MEDICATION - Continued

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experience section using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the start and end date.

Drug Name (Trade name preferred)	Unit Dose (e.g. 500mg)	Frequency (e.g. bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of a diagnosis)	Start Date (be as precise as possible)			End Date (or if continuing mark box)		
					Day	Mth	Yr	Day	Mth	Yr
For SB										
For SB										
For SB										
For SB										
For SB										
For SB										
For SB										
For SB										

* For Route, see tab for acceptable abbreviations.



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]	Visit Date Day Mth Yr [][][][][]	

MEDICAL PROCEDURES (Excluding treatment for COPD exacerbations)

Do not record procedures used to treat COPD exacerbations here, record them in the COPD Exacerbations section.

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed since the previous module ?

☐ No

☐ Yes —▶ If 'Yes', please record details below using standard medical terminology

All indications for procedures should be recorded in the Adverse Experience section.

Procedure	Indication	Procedure Start Date			Procedure End Date		
		Day	Mth	Yr	Day	Mth	Yr
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							



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Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy. All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages.**

If no COPD Exacerbations since the previous module, please sign form below and mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
End Date and Time (If ongoing please leave blank)	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
Outcome If patient died, STOP: go to SAE COPD Exacerbation pages	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent ☐ Constant	☐ Intermittent ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures section	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE ?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____		Date : Day Mth Yr



Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy. All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages.**

If no further COPD Exacerbations or changes to COPD Exacerbations have occurred since the previous study, please sign form below and mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
End Date and Time (If ongoing please leave blank)	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
Outcome If patient died, STOP: go to SAE COPD Exacerbation pages	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent ☐ Constant	☐ Intermittent ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures section	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE ?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Mth Yr	



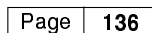
Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy. All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages.**

If no further COPD Exacerbations or changes to COPD Exacerbations have occurred since the previous study, please sign form below and mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
End Date and Time (If ongoing please leave blank)	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
Outcome If patient died, STOP: go to SAE COPD Exacerbation pages	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent ☐ Constant	☐ Intermittent ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures section	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE ?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Mth Yr	



Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date
207499/040				
				Day Mth Yr

Person Reporting SAE _____ (Please print clearly)		AEGIS Number . 	
Serious Adverse Experience		COPD Exacerbation	
For SmithKline Beecham		➤ Specify reason(s) for considering this a serious AE. Mark all that apply.	
Onset Date and Time	Day Mth Yr 24hr:min	fatal life threatening disabling/incapacitating results in hospitalisation (excluding elective surgery or routine clinical procedures) hospitalisation prolonged congenital abnormality cancer overdose Investigator considers serious or a significant hazard, contraindication, side effect or precaution	
End Date and Time (If ongoing please leave blank)	Day Mth Yr 24hr:min		
Outcome If patient died, please complete Form D	☐ Resolved ☐ Ongoing ☐ Died ➤ No. of episodes 		
Experience Course	☐ Intermittent ☐ Constant ➤ No. of episodes 		
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe		
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped		
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable ➤ Assessment The SAE is probably associated with : ☐ Protocol design or procedures (but not to study drug) Please specify _____ ☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____ ☐ Another drug Please specify _____		
Corrective Therapy If 'Yes', record details in the COPD Medication or Procedures pages	☐ Yes ☐ No		
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No		



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)

Relevant Laboratory Data

Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

If applicable, was randomisation code broken at investigational site ? ☐ No ☐ Yes

Randomisation / Study Medication Number : [][][][][]

Investigator's Signature : _____ **Date**

Day Mth Yr

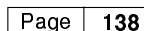
(confirming that the above data are accurate and complete)

Please PRINT name _____

SB Medical Monitor's Signature : _____ **Date**

Day Mth Yr

Please PRINT name _____



Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date
207499/040				
				Day Mth Yr

[illegible]



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)

Relevant Laboratory Data

Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

If applicable, was randomisation code broken at investigational site ? ☐ No ☐ Yes

Randomisation / Study Medication Number : [][][][][]

Investigator's Signature : _____ **Date**

Day Mth Yr

(confirming that the above data are accurate and complete)

Please PRINT name _____

SB Medical Monitor's Signature : _____ **Date**

Day Mth Yr

Please PRINT name _____

Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]		

MEDICATION FOR COPD EXACERBATIONS

Has the patient taken any medication for COPD exacerbations since the previous module ?

☐

No

☐

Yes → If 'Yes', please record details below

Drug Name (Trade name preferred)	Unit Dose (e.g. 500mg)	Frequency (e.g. bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of a diagnosis)	Start Date (be as precise as possible) Day Mth Yr	End Date (or if continuing mark box) Day Mth Yr	
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							

* For Route, see General Instructions for acceptable abbreviations.



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]		

MEDICAL PROCEDURES FOR COPD EXACERBATIONS

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since the previous module ?

☐ No

☐ Yes —▶ If 'Yes', please record details below using standard medical terminology

Procedure	Indication	Procedure Start Date			Procedure End Date		
		Day	Mth	Yr	Day	Mth	Yr
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							



Protocol 207499/040	Centre Number [][][][]	Patient Number [][][][][][]	Patient Initials [][][][]		

HEALTHCARE RESOURCE UTILISATION FOR COPD EXACERBATIONS

Complete this form for any **COPD exacerbation related medical care** the patient received since the previous module

Physician Visits (i.e., COPD care excluding scheduled protocol visits)

☐ There were no physician visits since the previous module

Date of Visit			Reason for Visit
Day	Mth	Yr	
[][][][][]			
[][][][][]			
[][][][][]			
[][][][][]			
[][][][][]			
[][][][][]			
[][][][][]			
[][][][][]			

Emergency Room (ER)/Urgent Care Visits/Casualty Department Procedures (i.e., lung surgery)

☐ There were no Emergency Room/Urgent Care Visits/Casualty Department Procedures since previous module

Date of Visit			Reason for Visit		Patient Admitted from ER ?	
					Yes	No
Day	Mth	Yr				
[][][][][]					☐	☐
[][][][][]					☐	☐
[][][][][]					☐	☐
[][][][][]					☐	☐
[][][][][]					☐	☐
[][][][][]					☐	☐
[][][][][]					☐	☐

Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]		

HEALTHCARE RESOURCE UTILISATION FOR COPD EXACERBATIONS - continued

Hospitalisations (also record details of any hospitalisations in the Serious Adverse Experience - COPD Exacerbation section)

☐ There were no hospitalisations since the previous module

Date of Admission			Date of Discharge			Reason for Admission
Day	Mth	Yr	Day	Mth	Yr	
[][][]	[][]	[][]	[][][]	[][]	[][]	
[][][]	[][]	[][]	[][][]	[][]	[][]	
[][][]	[][]	[][]	[][][]	[][]	[][]	
[][][]	[][]	[][]	[][][]	[][]	[][]	

Intensive Care Unit (ICU) stays (did the patient stay in the ICU during any of the above hospitalisations?)

☐ There were no ICU stays since the previous module

Date Admitted to ICU			Date Discharged from ICU			Reason for ICU Admission
Day	Mth	Yr	Day	Mth	Yr	
[][][]	[][]	[][]	[][][]	[][]	[][]	
[][][]	[][]	[][]	[][][]	[][]	[][]	
[][][]	[][]	[][]	[][][]	[][]	[][]	
[][][]	[][]	[][]	[][][]	[][]	[][]	

Lost Work Days (i.e., days patient missed work due to COPD excluding scheduled protocol visits)

☐ There were no lost work days since the previous module

Start Date			Stop Date			Reason for Absence
Day	Mth	Yr	Day	Mth	Yr	
[][][]	[][]	[][]	[][][]	[][]	[][]	
[][][]	[][]	[][]	[][][]	[][]	[][]	
[][][]	[][]	[][]	[][][]	[][]	[][]	
[][][]	[][]	[][]	[][][]	[][]	[][]	
[][][]	[][]	[][]	[][][]	[][]	[][]	
[][][]	[][]	[][]	[][][]	[][]	[][]	



Protocol	Centre Number	Patient Number	Patient Initials		
207499/040					

STUDY CONTINUATION / WITHDRAWAL

Is the patient continuing in the study ?

☐ Yes

☐ No → If 'No' please mark the **PRIMARY** cause of withdrawal and enter the date of the final visit and the date of the final dose.

1	☐ Adverse experience (complete AE form)
2	☐ Insufficient therapeutic effect
3	☐ Protocol deviation (including non-compliance)
4	☐ Lost to follow-up
5	☐ Other - specify:

Date of Final Visit

Day	Mth	Yr

Date of Final Dose

Day	Mth	Yr

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data on this case report form and that all information is complete and accurate.

Investigator's Signature

Date

Day	Mth	Yr

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)

SAEs MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS

COMPLETE THE SAE PAGES OPPOSITE

Please complete these pages as fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Experience Course' blank and update it later

SIGN AND DATE THE SAE PAGE**PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE**

- Demography
- Significant Medical/Surgical History and Physical Examination
- Study Medication Record
- Concomitant Medication
- Form D (if applicable)

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE

(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO :

Your local SB CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local SB CRA/Medical monitor within 24 hours



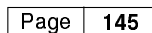
Protocol 207499/040	Centre Number 	Patient Number 			

MOD8 & MOD9 - SERIOUS ADVERSE EXPERIENCES

MOD8 & 9: Serious Adverse Experiences

MOD8 : 145, 146

MOD9 : 147, 148



Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date
207499/040				Day Mth Yr

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number																											
Serious Adverse Experience <i>(Please print clearly)</i>		➤ Specify reason(s) for considering this a serious AE. Mark all that apply. <table><tr><td>1</td><td>☐</td><td>fatal</td></tr><tr><td>2</td><td>☐</td><td>life threatening</td></tr><tr><td>3</td><td>☐</td><td>disabling/incapacitating</td></tr><tr><td>4</td><td>☐</td><td>results in hospitalisation (excluding elective surgery or routine clinical procedures)</td></tr><tr><td>5</td><td>☐</td><td>hospitalisation prolonged</td></tr><tr><td>6</td><td>☐</td><td>congenital abnormality</td></tr><tr><td>7</td><td>☐</td><td>cancer</td></tr><tr><td>8</td><td>☐</td><td>overdose</td></tr><tr><td>9</td><td>☐</td><td>Investigator considers serious or a significant hazard, contraindication, side effect or precaution</td></tr></table>	1	☐	fatal	2	☐	life threatening	3	☐	disabling/incapacitating	4	☐	results in hospitalisation (excluding elective surgery or routine clinical procedures)	5	☐	hospitalisation prolonged	6	☐	congenital abnormality	7	☐	cancer	8	☐	overdose	9	☐	Investigator considers serious or a significant hazard, contraindication, side effect or precaution
1	☐		fatal																										
2	☐		life threatening																										
3	☐		disabling/incapacitating																										
4	☐		results in hospitalisation (excluding elective surgery or routine clinical procedures)																										
5	☐		hospitalisation prolonged																										
6	☐		congenital abnormality																										
7	☐	cancer																											
8	☐	overdose																											
9	☐	Investigator considers serious or a significant hazard, contraindication, side effect or precaution																											
For SmithKline Beecham																													
Onset Date and Time	<table><tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr><tr><td>Day</td><td>Mth</td><td>Yr</td><td>24hr:</td><td>min</td><td></td></tr></table>							Day	Mth	Yr	24hr:	min																	
Day	Mth	Yr	24hr:	min																									
End Date and Time <i>(If ongoing please leave blank)</i>	<table><tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr><tr><td>Day</td><td>Mth</td><td>Yr</td><td>24hr:</td><td>min</td><td></td></tr></table>							Day	Mth	Yr	24hr:	min																	
Day	Mth	Yr	24hr:	min																									
Outcome <i>If patient died, please complete Form D</i>	<table><tr><td>☐</td><td>Resolved</td></tr><tr><td>☐</td><td>Ongoing</td></tr><tr><td>☐</td><td>Died</td></tr></table>	☐	Resolved	☐	Ongoing	☐	Died																						
☐	Resolved																												
☐	Ongoing																												
☐	Died																												
Experience Course	<table><tr><td>☐</td><td>Intermittent</td><td>➤ No. of episodes</td><td> </td></tr><tr><td>☐</td><td>Constant</td><td></td><td></td></tr></table>	☐	Intermittent	➤ No. of episodes		☐	Constant																						
☐	Intermittent	➤ No. of episodes																											
☐	Constant																												
Intensity <i>(maximum)</i>	<table><tr><td>☐</td><td>Mild</td></tr><tr><td>☐</td><td>Moderate</td></tr><tr><td>☐</td><td>Severe</td></tr></table>	☐	Mild	☐	Moderate	☐	Severe																						
☐	Mild																												
☐	Moderate																												
☐	Severe																												
Action Taken with Respect to Investigational Drug	<table><tr><td>☐</td><td>None</td></tr><tr><td>☐</td><td>Dose reduced</td></tr><tr><td>☐</td><td>Dose increased</td></tr><tr><td>☐</td><td>Drug interrupted/restarted</td></tr><tr><td>☐</td><td>Drug stopped</td></tr></table>	☐	None	☐	Dose reduced	☐	Dose increased	☐	Drug interrupted/restarted	☐	Drug stopped																		
☐	None																												
☐	Dose reduced																												
☐	Dose increased																												
☐	Drug interrupted/restarted																												
☐	Drug stopped																												
Relationship to Investigational Drug	<table><tr><td>☐</td><td>Not related</td></tr><tr><td>☐</td><td>Unlikely</td></tr><tr><td>☐</td><td>Suspected (reasonable possibility)</td></tr><tr><td>☐</td><td>Probable</td></tr></table>	☐	Not related	☐	Unlikely	☐	Suspected (reasonable possibility)	☐	Probable																				
☐	Not related																												
☐	Unlikely																												
☐	Suspected (reasonable possibility)																												
☐	Probable																												
Corrective Therapy <i>If 'Yes', record details in the Concomitant Medication section</i>	<table><tr><td>☐</td><td>Yes</td><td>☐</td><td>No</td></tr></table>	☐	Yes	☐	No																								
☐	Yes	☐	No																										
Was patient withdrawn due to this specific SAE ?	<table><tr><td>☐</td><td>Yes</td><td>☐</td><td>No</td></tr></table>	☐	Yes	☐	No																								
☐	Yes	☐	No																										



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data**

Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

If applicable, was randomisation code broken at investigational site ? ☐ No ☐ Yes

Randomisation / Study Medication Number : [][][][][]

Investigator's Signature : _____ **Date**

Day Mth Yr

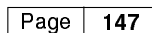
(confirming that the above data are accurate and complete)

Please PRINT name _____

SB Medical Monitor's Signature : _____ **Date**

Day Mth Yr

Please PRINT name _____



Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date
207499/040				Day Mth Yr

Person Reporting SAE _____ (Please print clearly)		AEGIS Number . 	
Serious Adverse Experience (Please print clearly)		➤ Specify reason(s) for considering this a serious AE. Mark all that apply.	
For SmithKline Beecham		1 ☐ fatal 2 ☐ life threatening 3 ☐ disabling/incapacitating 4 ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) 5 ☐ hospitalisation prolonged 6 ☐ congenital abnormality 7 ☐ cancer 8 ☐ overdose 9 ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution	
Onset Date and Time	Day Mth Yr 24hr:min		
End Date and Time (If ongoing please leave blank)	Day Mth Yr 24hr:min		
Outcome If patient died, please complete Form D	☐ Resolved ☐ Ongoing ☐ Died		
Experience Course	☐ Intermittent ➤ No. of episodes ☐ Constant		
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe		
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate ? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased) ☐ Yes ☐ No If yes, did SAE recur ☐ Yes ☐ No	
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	➤ Assessment The SAE is probably associated with : ☐ Protocol design or procedures (but not to study drug) Please specify _____ ☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____ ☐ Another drug Please specify _____	
Corrective Therapy If 'Yes', record details in the Concomitant Medication section	☐ Yes ☐ No		
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No		



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data**

Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

If applicable, was randomisation code broken at investigational site ? ☐ No ☐ Yes

Randomisation / Study Medication Number : [][][][][]

Investigator's Signature : _____ **Date**

Day Mth Yr

(confirming that the above data are accurate and complete)

Please PRINT name _____

SB Medical Monitor's Signature : _____ **Date**

Day Mth Yr

Please PRINT name _____

Protocol	Centre Number	Patient Number	Patient Initials
207499/040			

CONFIDENTIAL



PROTOCOL SB 207499/040

BOOK 4 : VISITS 9 AND 10 (WEEKS 24 AND 28)

**A MULTICENTRE, OPEN-LABEL EXTENSION STUDY
TO EVALUATE THE SAFETY, TOLERABILITY AND EFFICACY
OF ORAL SB 207499 (15mg TWICE DAILY) IN PATIENTS WITH
CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)**

GENERAL INSTRUCTIONS

- Write clearly in capital letters using a black ball point pen and press firmly so that all copies are legible
- Do not write in shaded areas
- Answer ALL questions on every page
- Enter "N/A" if information requested is not available
- Initial and date all changes, additions or deletions. Use a single pen stroke to remove an incorrect entry
- Enter the patient initials on all pages on which information has been entered and the patient number and centre number where required
- Do not enter additional data/information after the set of CRF pages has been split/separated
- The cover flap or plastic writing board should be used to divide each set of pages before writing on them with a ball point pen

DATE

Please use the following three-letter abbreviations for the months :

January	JAN
February	FEB
March	MAR
April	APR
May	MAY
June	JUN
July	JUL
August	AUG
September	SEP
October	OCT
November	NOV
December	DEC

e.g.

0	1	J	A	N	9	9
Day		Mth			Yr	

 = 1st January 1999

TIME

Unless specified otherwise, please use the 24 hour clock :

e.g.

1	5	3	0
24hr		min	

 = 3.30 p.m.

PATIENT INITIALS

Please use the following format ;

e.g. XXXXXXXXXX

ROUTE KEY FOR PRIOR/CONCOMITANT MEDICATION PAGE

PO = By mouth	SL = Sublingual	TD = Transdermal
IV = Intravenous	IT = Intrathecal	IH = Inhaled
IM = Intramuscular	VA = Vaginal	SC = Subcutaneous
IAR = Intra-arterial	NA = Nasal	PR = Rectal
TO = Topical	IA = Intra-articular injection	ID = Intradermal

SUMMARY CHART OF STUDY PROCEDURES (OPEN BOXES)
PROTOCOL SB 207499/040

Mark open boxes to confirm that each procedure has been completed.

Procedures	Visit 9	Visit 10
	Week 24	Week 28
Signed written informed consent		
Study Medication compliance		
Concomitant Medication		
Diary Card Review ⁷		
Adverse Experiences ⁸		
COPD Exacerbation assessment/Healthcare Ut.		
Physical (Including Respiratory) Examination		
Resting 12-Lead ECG		
Vital Signs (BP, HR) ³		
Overall Breathlessness (Modified Borg)		
Exercise Tolerance Test - 6 Minute Walk		
Post Exercise Breathlessness		
Pulmonary Function Tests ⁴		
Laboratory Tests ⁵		
Pregnancy Test ⁶		
Quality of Life Assessment: SGRQ		
Quality of Life Assessment: SF-36		
Dispense or re-dispense Open-Label Medication		
Study Continuation / Withdrawal		

³ Orthostatic blood pressure and heart rate are measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal.

⁴ To include FEV₁, FEV₆, FVC, FEF₂₅₋₇₅, FEF₇₅, and PEFR.

⁵ Faecal occult blood is measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal. Baseline measure is taken from last FOB in Study 042 or Study 091.

⁶ Serum pregnancy test for female patients of child bearing potential. Urine test only is done at Follow-Up Visit.

⁷ A Diary Card is issued at each visit. The patient will use the Diary Card to record if they feel differently since the previous visit.

⁸ Patients will be assessed for GI AEs at every visit.



Protocol	Centre Number	Patient Number			
207499/040					

MODULE 10

Module 10: Visit 9 (Week 24) and Visit 10 (Week 28), Adverse Experiences, Conmeds, Medical Procedures, COPD Exacerbations, Resource Utilisation, Continuation/Withdrawal.

CRF Pages: 149 - 190

Unprocessed forms: Within this module the following occur which will generate attachments that need to be brought in-house.

Visit 9

St Georges Respiratory Questionnaire

SF-36



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]	Visit Date Day Mth Yr [][][][][]	Visit 9 Week 24

PRESENTATION TO CLINIC

Record time of presentation to clinic [][][]
24hr:min

Note : Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.

Record the date and time of the patient's last dose of short-acting beta₂ agonist [][][][][] [][][]
Day Mth Yr 24hr:min

Record the date and time of the patient's last dose of long-acting beta₂ agonist [][][][][] [][][]
Day Mth Yr 24hr:min

Record the date and time of the patient's last dose of anticholinergic [][][][][] [][][]
Day Mth Yr 24hr:min

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes → If 'Yes' please record time [][][]
24hr:min

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 9 Week 24

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐

No

☐

Yes —► If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	Day Mth Yr	Day Mth Yr	Day Mth Yr	Day Mth Yr
Level of exacerbation (maximum intensity)	☐ Level 1	☐ Level 1	☐ Level 1	☐ Level 1
	☐ Level 2	☐ Level 2	☐ Level 2	☐ Level 2
	☐ Level 3	☐ Level 3	☐ Level 3	☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 9 Week 24

RESOURCE UTILISATION FOR COPD EXACERBATIONS

If the patient has received any COPD exacerbation related medical care since the previous visit, please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

*Review the diary card for illegible/incomplete entries **in the presence of the patient.***

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a clinically significant worsening in the patient's physical condition since the previous examination ?

☐

No

☐

Yes



If 'Yes' record details in the Adverse Experience section at the back of this module.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 9 Week 24

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)

Date and time of last dose of study medication prior to the study visit

Day	Mth	Yr	24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70					

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤ 120%?

- ☐ No → If 'No' please check the % compliance at the previous visit. If compliance was not ≥ 80% and ≤ 120% at the last visit, please withdraw the patient. Please complete the assessments for Visit 9 and the assessments for patients withdrawing or stopping the study at Visit 9, contained at the end of this visit.
- ☐ Yes



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 9 Week 24

SMOKING STATUS

Does the patient currently smoke ?

☐

No

☐

Yes



If 'Yes' please record the average number of cigarettes per day :

PULMONARY REHABILITATION PROGRAMME

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit ?

☐

No

☐

Yes

LABORATORY TESTS

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential). Please refer to the instructions on the SBCL shipping form and manual.

Blood Sample Date

Day
Mth
Yr

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below.

Attach label here

Are there any **clinically significant worsenings** since the previous visit ?

☐

No

☐

Yes



If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

Place the SBCL laboratory report in the plastic wallet at the back of this module.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 9 Week 24

URINALYSIS

Please perform urinalysis using the dipstick provided by SBCL and record the results in the patient notes.

Urine Sample Date
Day Mth Yr

Are the dipstick results negative?

- ☐ No —▶ If 'No' please send the sample to SBCL for microscopy
☐ Yes

Are there any **clinically significant worsenings** since the previous visit on the SBCL report?

- ☐ No
☐ Yes —▶ If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

PREGNANCY TEST

Is the patient a female of child-bearing potential ?

- ☐ No
☐ Yes —▶ If 'Yes' please request a pregnancy test on the SBCL requisition form.

Is the patient pregnant?

- ☐ No
☐ Yes —▶ If 'Yes' please withdraw the patient from the study, enter details in the Adverse Experience section. Complete the Early Withdrawal Visit (found as a separate book).



Protocol 207499/040		Patient Number <table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>						Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						Visit 9 Week 24

OVERALL BREATHLESSNESS ASSESSMENT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 9 Week 24

INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)

Are there any **clinically significant worsenings** since the last visit ?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed:
Day Mth Yr

Were any clinically significant changes noted since the last visit ?

☐ No

☐ Yes → ☐ Improvement

☐ Worsening → *Enter details in the Adverse Experience section at the back of this module.*

Place the ECG trace in the plastic wallet at the back of this module.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 9 Week 24

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement : After 5 Minutes Supine

Blood Pressure mmHg systolic / diastolic	Heart Rate beats/min
/	

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure mmHg systolic / diastolic	Heart Rate beats/min
/	

Are there any **clinically significant worsenings** since the previous assessment ?

☐

No

☐

Yes



If 'Yes' record details in the Adverse Experience section at the back of this module.



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Protocol 207499/040		Patient Number 	Patient Initials 		Visit 9 Week 24

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted ? *The distance walked should be entered even if the patient did not walk for 6 minutes. If the patient was too ill to attempt the test, please mark the 'Yes' box and enter 0 for distance walked.*

☐ No

☐ Yes → if 'Yes', Distance walked Metres

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

POST-EXERCISE BREATHLESSNESS (Immediately after the patient completes the exercise tolerance)
Heart Rate beats/min
Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

- 0 Nothing at all
- 1 Very, very slight (just noticeable)
- 2 Very slight
- 3 Moderate
- 4 Somewhat severe
- 5 Severe
- 6
- 7 Very severe
- 8
- 9 Very, very severe (almost maximal)
- 10 Maximal

Post-exercise breathlessness score .
INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise tolerance test (rest for at least 10 minutes) before performing the pulmonary function tests.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 9 Week 24

PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and / or anticholinergic medications and / or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

STUDY MEDICATION LABEL

Issue the patient one bottle of open-label study medication (70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

Attach study medication
label here

Give the patient the first dose of study medication with food and record the date and time of administration below.

Date and time of administration

Day	Mth	Yr	24hr:min				



Protocol		Patient Number	Patient Initials		Visit 9 Week 24
207499/040					

INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐ No —→ If 'No' please complete the assessments for Visit 9 and issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-Up Visit. Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return in 7 +/- 3 days for a Follow-Up Visit.

☐ Yes —→ If 'Yes' please;

- Issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the next visit.
- Issue a new diary card. Remind the patient to record if they feel differently since starting the study.
- Ask the patient to return for the next visit in 28 +/- 6 days.
- **Remind the patient:**
 - i to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.
 - ii **not** to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).
 - iii to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonist (long-acting) for **12 hours** before the next visit.
 - iv to refrain from smoking for **2 hours** immediately preceding the visit.
 - v to bring any remaining study medication or study medication containers and the diary card.
 - vi to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.



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Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]	Visit Date Day Mth Yr [][][][][]	Visit 10 Week 28

PRESENTATION TO CLINIC

Record time of presentation to clinic [][][]
24hr:min

Note: Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.

Record the date and time of the patient's last dose of short-acting beta₂ agonist [][][][][][] 24hr:min
Day Mth Yr

Record the date and time of the patient's last dose of long-acting beta₂ agonist [][][][][][] 24hr:min
Day Mth Yr

Record the date and time of the patient's last dose of anticholinergic [][][][][][] 24hr:min
Day Mth Yr

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes → If 'Yes' please record time [][][] 24hr:min

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	[][][][][][] Day Mth Yr	[][][][][][] Day Mth Yr	[][][][][][] Day Mth Yr	[][][][][][] Day Mth Yr
Level of exacerbation (maximum intensity)	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 10 Week 28

RESOURCE UTILISATION FOR COPD EXACERBATIONS

Please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

Review the diary card for illegible/incomplete entries **in the presence of the patient**.

ADVERSE EXPERIENCES

Please complete the Adverse Experience section at the back of this module. If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

Please complete the Concomitant Medication section at the back of this module. If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 10 Week 28

FAECAL OCCULT BLOOD TEST

Record the results of the faecal occult blood tests performed between Visits 9 and 10.

Test	Date of Collection	Was the faecal occult blood test positive?
	Day Mth Yr	
1		☐ No ☐ Yes
2		☐ No ☐ Yes
3		☐ No ☐ Yes

Are these findings clinically significant ?

☐

No

☐

Yes



If 'Yes' record details in the Adverse Experience section at the back of this module.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 10 Week 28

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)

Date and time of last dose of study medication prior to the study visit

Day Mth Yr

24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70					

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤ 120%?

- ☐ No → If 'No' please check the % compliance at the previous visit. If compliance was not ≥ 80% and ≤ 120% at the last visit, please withdraw the patient. Please complete the assessments for Visit 10 and the assessments for patients withdrawing or stopping the study at Visit 10, contained at the end of this visit.
- ☐ Yes



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 10 Week 28

SMOKING STATUS

Does the patient currently smoke ?

☐

No

☐

Yes



If 'Yes' please record the average number of cigarettes per day :

PULMONARY REHABILITATION PROGRAMME

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit ?

☐

No

☐

Yes

LABORATORY TESTS

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential). Please refer to the instructions on the SBCL shipping form and manual.

Blood Sample Date

Day
Mth
Yr

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below.

Attach label here

Are there any **clinically significant worsenings** since the previous visit ?

☐

No

☐

Yes



If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

Place the SBCL laboratory report in the plastic wallet at the back of this module.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 10 Week 28

URINALYSIS

Please perform urinalysis using the dipstick provided by SBCL and record the results in the patient notes.

Urine Sample Date
Day Mth Yr

Are the dipstick results negative?

- ☐ No —▶ If 'No' please send the sample to SBCL for microscopy
☐ Yes

Are there any **clinically significant worsenings** since the previous visit on the SBCL report?

- ☐ No
☐ Yes —▶ If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

PREGNANCY TEST

Is the patient a female of child-bearing potential ?

- ☐ No
☐ Yes —▶ If 'Yes' please request a pregnancy test on the SBCL requisition form.

Is the patient pregnant?

- ☐ No
☐ Yes —▶ If 'Yes' please withdraw the patient from the study, enter details in the Adverse Experience section. Complete the Early Withdrawal Visit (found as a separate book).



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OVERALL BREATHLESSNESS ASSESSMENT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 10 Week 28

INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)

Are there any **clinically significant worsenings** since the last visit ?

☐

No

☐

Yes



If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed:

Day	Mth	Yr	

Were any clinically significant changes noted since the last visit ?

☐

No

☐

Yes


☐

Improvement

☐

Worsening



Enter details in the Adverse Experience section at the back of this module.

Place the ECG trace in the plastic wallet at the back of this module.



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 10 Week 28

PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and / or anticholinergic medications and / or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

STUDY MEDICATION LABEL

Issue the patient one bottle of open-label study medication (70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

Attach study medication
label here

Give the patient the first dose of study medication with food and record the date and time of administration below.

Date and time of administration
Day Mth Yr 24hr:min



Protocol 207499/040		Patient Number 	Patient Initials 		Visit 10 Week 28

INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐ No —► If 'No' please complete the assessments for Visit 10 and the Assessments for Patients Withdrawing or Stopping the Study at Visit 10 contained on the following pages. Complete and fax the Withdrawal Form contained in the Withdrawal and Follow-Up Book.

☐ Yes —► If 'Yes' please;

- Issue a new diary card. Remind the patient to record if they feel differently since starting the study.
- Ask the patient to return for the next visit in 28 +/- 6 days.
- Complete the Study Continuation / Withdrawal page at the back of this module.
- **Remind the patient:**
 - i to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.
 - ii **not** to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).
 - iii to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonists (long-acting) for **12 hours** before the next visit.
 - iv to refrain from smoking for **2 hours** immediately preceding the visit.
 - v to bring any remaining study medication or study medication containers and the diary card.
 - vi to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.



Protocol		Patient Number	Patient Initials		Visit 10 Week 28
207499/040					

ASSESSMENTS FOR PATIENTS WITHDRAWING OR STOPPING THE STUDY

Complete the assessments below only for patients who are withdrawing early from the study or stopping the study because the product has been registered or because the sponsor has terminated the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a clinically significant worsening in the patient's physical condition since the previous examination ?

☐

No

☐

Yes



If 'Yes' record details in the Adverse Experience section at the back of this module.



Protocol 207499/040		Patient Number [][][][][]	Patient Initials [][][][]		Visit 10 Week 28

FAECAL OCCULT BLOOD TEST

Issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-up Visit.

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement : After 5 Minutes Supine

Blood Pressure mmHg systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure mmHg systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the previous assessment ?

☐

No

☐

Yes



If 'Yes' record details in the Adverse Experience section at the back of this module.

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Follow-Up Visit in 7 +/- 3 days.

ADVERSE EXPERIENCES (Non-serious)**DEFINITIONS****INTENSITY (Maximum)**

MILD	<i>Adverse experience which is easily tolerated</i>
MODERATE	<i>Adverse experience sufficiently discomforting to interfere with daily activity</i>
SEVERE	<i>Adverse experience which prevents normal everyday activities</i>

RELATIONSHIP TO INVESTIGATIONAL DRUG

NOT RELATED	<i>The adverse experience is definitely not related to the test drug</i>
UNLIKELY	<i>There are other more likely causes and the drug is not suspected as a cause</i>
SUSPECTED (REASONABLE POSSIBILITY)	<i>A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug</i>
PROBABLE	<i>There probably is a direct cause and effect relationship between the adverse experience and the study drug</i>

SERIOUS ADVERSE EXPERIENCE (SAE)

A SAE is any experience which is :-

- 1 - fatal
- 2 - life threatening
- 3 - disabling/incapacitating
- 4 - results in hospitalisation (excluding elective surgery or routine clinical procedures)
- 5 - prolongs a hospital stay
- 6 - associated with congenital abnormality
- 7 - cancer
- 8 - associated with overdose
- 9 - In addition any event which the investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug should be reported as a serious event

IF A SAE OCCURS, PLEASE GO TO THE SAE SECTION IMMEDIATELY AND FOLLOW THE INSTRUCTIONS GIVEN THERE

Use each form for a maximum of two experiences

PLEASE REMEMBER ALL QUESTIONS ON ADVERSE EXPERIENCES FORM SHOULD BE COMPLETED



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Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Do you feel different in any way since starting the treatment or since the previous module?" Provide the diagnosis **not** symptoms where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbation section.

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the SAE section (See opposite for definitions of an SAE).

If no adverse experiences occurred since the previous module, please sign form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Mth Yr 24hr:min	 Day Mth Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Mth Yr 24hr:min	 Day Mth Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy <i>If 'Yes', record details in the Concomitant Medication and / or Medical Procedures section</i> ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Mth Yr	

Protocol 207499/040	Centre Number [][][][]	Patient Number [][][][][]	Patient Initials [][][][]		

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Do you feel different in any way since starting the treatment or since the previous module?" Provide the diagnosis **not** symptoms where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbation section.

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the SAE section (See opposite for definitions of an SAE).

If no further adverse experiences or changes in adverse experiences occurred since the previous module, please sign form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	[][][][] [][][][] Day Mth Yr 24hr:min	[][][][] [][][][] Day Mth Yr 24hr:min
End Date and Time (If ongoing please leave blank)	[][][][] [][][][] Day Mth Yr 24hr:min	[][][][] [][][][] Day Mth Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of [][] episodes ☐ Constant	☐ Intermittent → No. of [][] episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy <i>If 'Yes', record details in the Concomitant Medication and / or Medical Procedures section</i> ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE ?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : [][][] [][][] [][][] Day Mth Yr	

Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Do you feel different in any way since starting the treatment or since the previous module?" Provide the diagnosis **not** symptoms where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbation section.

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the SAE section (See opposite for definitions of an SAE).

If no further adverse experiences or changes in adverse experiences occurred since the previous module, please sign form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Mth Yr 24hr:min	 Day Mth Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Mth Yr 24hr:min	 Day Mth Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy <i>If 'Yes', record details in the Concomitant Medication and / or Medical Procedures section</i> ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE ?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Mth Yr	



Protocol	Centre Number	Patient Number	Patient Initials		
207499/040					

CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the previous module.
(Please write using BLOCK CAPITALS)

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

☐ No concomitant medication changes since the previous module

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experience section using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the start and end date.

Drug Name (Trade name preferred)	Unit Dose (e.g. 500mg)	Frequency (e.g. bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of a diagnosis)	Start Date (be as precise as possible)			End Date (or if continuing mark box)			▼
					Day	Mth	Yr	Day	Mth	Yr	
											☐
For SB											
											☐
For SB											
											☐
For SB											
											☐
For SB											
											☐
For SB											
											☐
For SB											
											☐
For SB											
											☐
For SB											

* For Route, see tab for acceptable abbreviations.



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][]		

CONCOMITANT MEDICATION - Continued

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experience section using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the start and end date.

Drug Name (Trade name preferred)	Unit Dose (e.g. 500mg)	Frequency (e.g. bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of a diagnosis)	Start Date (be as precise as possible)			End Date (or if continuing mark box)		
					Day	Mth	Yr	Day	Mth	Yr
					[][][][][]	[][][][][]	[][][][][]	[][][][][]	[][][][][]	[]
For SB										
					[][][][][]	[][][][][]	[][][][][]	[][][][][]	[][][][][]	[]
For SB										
					[][][][][]	[][][][][]	[][][][][]	[][][][][]	[][][][][]	[]
For SB										
					[][][][][]	[][][][][]	[][][][][]	[][][][][]	[][][][][]	[]
For SB										
					[][][][][]	[][][][][]	[][][][][]	[][][][][]	[][][][][]	[]
For SB										
					[][][][][]	[][][][][]	[][][][][]	[][][][][]	[][][][][]	[]
For SB										
					[][][][][]	[][][][][]	[][][][][]	[][][][][]	[][][][][]	[]
For SB										
					[][][][][]	[][][][][]	[][][][][]	[][][][][]	[][][][][]	[]
For SB										

* For Route, see tab for acceptable abbreviations.



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][][]	Patient Initials [][][][]	Visit Date Day Mth Yr [][][][][]	

MEDICAL PROCEDURES (Excluding treatment for COPD exacerbations)

Do not record procedures used to treat COPD exacerbations here, record them in the COPD Exacerbations section.

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed since the previous module ?

☐ No

☐ Yes —▶ If 'Yes', please record details below using standard medical terminology

All indications for procedures should be recorded in the Adverse Experience section.

Procedure	Indication	Procedure Start Date			Procedure End Date		
		Day	Mth	Yr	Day	Mth	Yr
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							



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Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy. All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages.**

If no COPD Exacerbations since the previous module, please sign form below and mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
End Date and Time (If ongoing please leave blank)	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
Outcome If patient died, STOP: go to SAE COPD Exacerbation pages	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent ☐ Constant	☐ Intermittent ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures section	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE ?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Mth Yr	



Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy. All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages.**

If no further COPD Exacerbations or changes to COPD Exacerbations have occurred since the previous study, please sign form below and mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
End Date and Time (If ongoing please leave blank)	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
Outcome If patient died, STOP: go to SAE COPD Exacerbation pages	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent ☐ Constant	☐ Intermittent ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures section	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE ?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Mth Yr	



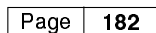
Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy. All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages.**

If no further COPD Exacerbations or changes to COPD Exacerbations have occurred since the previous study, please sign form below and mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
End Date and Time (If ongoing please leave blank)	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
Outcome If patient died, STOP: go to SAE COPD Exacerbation pages	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent ☐ Constant	☐ Intermittent ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures section	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE ?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Mth Yr	



Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date
207499/040				Day Mth Yr

Person Reporting SAE _____ (Please print clearly)		AEGIS Number . 	
Serious Adverse Experience		COPD Exacerbation	
For SmithKline Beecham		➤ Specify reason(s) for considering this a serious AE. Mark all that apply.	
Onset Date and Time	Day Mth Yr 24hr:min	fatal life threatening disabling/incapacitating results in hospitalisation (excluding elective surgery or routine clinical procedures) hospitalisation prolonged congenital abnormality cancer overdose Investigator considers serious or a significant hazard, contraindication, side effect or precaution	
End Date and Time (If ongoing please leave blank)	Day Mth Yr 24hr:min		
Outcome If patient died, please complete Form D	Resolved Ongoing Died		
Experience Course	Intermittent Constant ➤ No. of episodes 		
Intensity (maximum)	Mild Moderate Severe		
Action Taken with Respect to Investigational Drug	None Dose reduced Dose increased Drug interrupted/restarted Drug stopped		
Relationship to Investigational Drug	Not related Unlikely Suspected (reasonable possibility) Probable		
Corrective Therapy If 'Yes', record details in the COPD Medication or Procedures pages	Yes No		
Was patient withdrawn due to this specific SAE ?	Yes No		
		Did the SAE abate ? Yes No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased) Yes No If yes, did SAE recur Yes No	
		Assessment The SAE is probably associated with : Protocol design or procedures (but not to study drug) Please specify _____ Another condition (eg, condition under study, intercurrent illness) Please specify _____ Another drug Please specify _____	



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)

Relevant Laboratory Data

Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

If applicable, was randomisation code broken at investigational site ? ☐ No ☐ Yes

Randomisation / Study Medication Number : [][][][][]

Investigator's Signature : _____ **Date**

Day Mth Yr

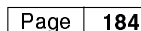
(confirming that the above data are accurate and complete)

Please PRINT name _____

SB Medical Monitor's Signature : _____ **Date**

Day Mth Yr

Please PRINT name _____



Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date
207499/040				
				Day Mth Yr

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience	COPD Exacerbation	➤ Specify reason(s) for considering this a serious AE. Mark all that apply. 1 2 3 4 5 6 7 8 9 ☐ fatal ☐ life threatening ☐ disabling/incapacitating ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) ☐ hospitalisation prolonged ☐ congenital abnormality ☐ cancer ☐ overdose ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	 Day Mth Yr 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	 Day Mth Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent ➤ No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate ? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased) ☐ Yes ☐ No If yes, did SAE recur ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	➤ Assessment The SAE is probably associated with : ☐ Protocol design or procedures (but not to study drug) <i>Please specify</i> _____ ☐ Another condition (eg, condition under study, intercurrent illness) <i>Please specify</i> _____ ☐ Another drug <i>Please specify</i> _____
Corrective Therapy <i>If 'Yes', record details in the COPD Medication or Procedures pages</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)

Relevant Laboratory Data

Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

If applicable, was randomisation code broken at investigational site ? ☐ No ☐ Yes

Randomisation / Study Medication Number : [][][][][]

Investigator's Signature : _____ **Date**

Day Mth Yr

(confirming that the above data are accurate and complete)

Please PRINT name _____

SB Medical Monitor's Signature : _____ **Date**

Day Mth Yr

Please PRINT name _____

Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]		

MEDICATION FOR COPD EXACERBATIONS

Has the patient taken any medication for COPD exacerbations since the previous module ?

- ☐ No
☐ Yes → If 'Yes', please record details below

Drug Name (Trade name preferred)	Unit Dose (e.g. 500mg)	Frequency (e.g. bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of a diagnosis)	Start Date (be as precise as possible) Day Mth Yr	End Date (or if continuing mark box) Day Mth Yr	
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							

* For Route, see General Instructions for acceptable abbreviations.



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]		

MEDICAL PROCEDURES FOR COPD EXACERBATIONS

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since the previous module ?

☐ No

☐ Yes —▶ If 'Yes', please record details below using standard medical terminology

Procedure	Indication	Procedure Start Date			Procedure End Date		
		Day	Mth	Yr	Day	Mth	Yr
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							



Protocol	Centre Number	Patient Number	Patient Initials		
207499/040					

HEALTHCARE RESOURCE UTILISATION FOR COPD EXACERBATIONS

Complete this form for any **COPD exacerbation related medical care** the patient received since the previous module

Physician Visits (i.e., COPD care excluding scheduled protocol visits)

☐ There were no physician visits since the previous module

Date of Visit	Reason for Visit
Day Mth Yr	

Emergency Room (ER)/Urgent Care Visits/Casualty Department Procedures (i.e., lung surgery)

☐ There were no Emergency Room/Urgent Care Visits/Casualty Department Procedures since previous module

Date of Visit	Reason for Visit	Patient Admitted from ER ?	
Day Mth Yr		Yes	No
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐
		☐	☐

Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]		

HEALTHCARE RESOURCE UTILISATION FOR COPD EXACERBATIONS - continued

Hospitalisations (also record details of any hospitalisations in the Serious Adverse Experience - COPD Exacerbation section)

☐ There were no hospitalisations since the previous module

Date of Admission			Date of Discharge			Reason for Admission
Day	Mth	Yr	Day	Mth	Yr	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	

Intensive Care Unit (ICU) stays (did the patient stay in the ICU during any of the above hospitalisations?)

☐ There were no ICU stays since the previous module

Date Admitted to ICU			Date Discharged from ICU			Reason for ICU Admission
Day	Mth	Yr	Day	Mth	Yr	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	

Lost Work Days (i.e., days patient missed work due to COPD excluding scheduled protocol visits)

☐ There were no lost work days since the previous module

Start Date			Stop Date			Reason for Absence
Day	Mth	Yr	Day	Mth	Yr	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	



Protocol	Centre Number	Patient Number	Patient Initials		
207499/040					

STUDY CONTINUATION / WITHDRAWAL

Is the patient continuing in the study ?

☐ Yes

☐ No —→ If 'No' please mark the **PRIMARY** cause of withdrawal and enter the date of the final visit and the date of the final dose.

1	☐ Adverse experience (complete AE form)
2	☐ Insufficient therapeutic effect
3	☐ Protocol deviation (including non-compliance)
4	☐ Lost to follow-up
5	☐ Other - specify:

Date of Final Visit

Day	Mth	Yr

Date of Final Dose

Day	Mth	Yr

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data on this case report form and that all information is complete and accurate.

Investigator's Signature Date

Day	Mth	Yr

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)

SAEs MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS

COMPLETE THE SAE PAGES OPPOSITE

Please complete these pages as fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Experience Course' blank and update it later

SIGN AND DATE THE SAE PAGE**PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE**

- Demography
- Significant Medical/Surgical History and Physical Examination
- Study Medication Record
- Concomitant Medication
- Form D (if applicable)

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE

(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO :

Your local SB CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local SB CRA/Medical monitor within 24 hours



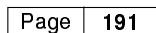
Protocol	Centre Number	Patient Number			
207499/042					

MOD11 & MOD12 - SERIOUS ADVERSE EXPERIENCES

MOD11 & 12: Serious Adverse Experiences

MOD11 : 191, 192

MOD12 : 193, 194



Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date
207499/040				
				Day Mth Yr

Person Reporting SAE _____ (Please print clearly)		AEGIS Number 	
Serious Adverse Experience (Please print clearly)	➔ Specify reason(s) for considering this a serious AE. Mark all that apply.		
For SmithKline Beecham	1 ☐ fatal 2 ☐ life threatening 3 ☐ disabling/incapacitating 4 ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) 5 ☐ hospitalisation prolonged 6 ☐ congenital abnormality 7 ☐ cancer 8 ☐ overdose 9 ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution		
Onset Date and Time	Day Mth Yr	24hr:min	
End Date and Time (If ongoing please leave blank)	Day Mth Yr	24hr:min	
Outcome If patient died, please complete Form D	☐ Resolved ☐ Ongoing ☐ Died		
Experience Course	☐ Intermittent ☐ Constant	➔ No. of episodes 	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe		
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped		
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable		
Corrective Therapy If 'Yes', record details in the Concomitant Medication section	☐ Yes ☐ No		
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No		



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data**

Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

If applicable, was randomisation code broken at investigational site ? ☐ No ☐ Yes

Randomisation / Study Medication Number : [][][][][]

Investigator's Signature : _____ **Date**

Day Mth Yr

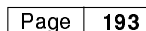
(confirming that the above data are accurate and complete)

Please PRINT name _____

SB Medical Monitor's Signature : _____ **Date**

Day Mth Yr

Please PRINT name _____



Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date
207499/040				Day Mth Yr

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience <i>(Please print clearly)</i>		➤ Specify reason(s) for considering this a serious AE. Mark all that apply. 1 2 3 4 5 6 7 8 9 ☐ fatal ☐ life threatening ☐ disabling/incapacitating ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) ☐ hospitalisation prolonged ☐ congenital abnormality ☐ cancer ☐ overdose ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	/ / Day Mth Yr : 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	/ / Day Mth Yr : 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent ➤ No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate ? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased) ☐ Yes ☐ No If yes, did SAE recur ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	➤ Assessment The SAE is probably associated with : ☐ Protocol design or procedures (but not to study drug) <i>Please specify</i> _____ ☐ Another condition (eg, condition under study, intercurrent illness) <i>Please specify</i> _____ ☐ Another drug <i>Please specify</i> _____
Corrective Therapy <i>If 'Yes', record details in the Concomitant Medication section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data**

Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

If applicable, was randomisation code broken at investigational site ? ☐ No ☐ Yes

Randomisation / Study Medication Number : [][][][][]

Investigator's Signature : _____ **Date**

Day Mth Yr

(confirming that the above data are accurate and complete)

Please PRINT name _____

SB Medical Monitor's Signature : _____ **Date**

Day Mth Yr

Please PRINT name _____

Protocol	Centre Number	Patient Number	Patient Initials
207499/040		0 0 0 0 0	

CONFIDENTIAL*PROTOCOL 207499/040**BOOK 5 : VISITS 11 AND 12 (WEEKS 32 AND 36)*

***A MULTICENTRE, OPEN-LABEL EXTENSION STUDY TO EVALUATE
THE SAFETY, TOLERABILITY AND EFFICACY OF ORAL SB 207499
(15mg TWICE DAILY) IN PATIENTS WITH CHRONIC OBSTRUCTIVE
PULMONARY DISEASE (COPD)***

GENERAL INSTRUCTIONS

- Write clearly in capital letters using a black ball point pen and press firmly so that all copies are legible
- Do not write in shaded areas
- Answer ALL questions on every page
- Enter "N/A" if information requested is not available
- Initial and date all changes, additions or deletions. Use a single pen stroke to remove an incorrect entry
- Enter the patient initials on all pages on which information has been entered and the patient number and centre number where required

Do not enter additional data/information after the set of CRF pages has been split/separated

The cover flap or plastic writing board should be used to divide each set of pages before writing on them with a ball point pen

DATE

Please use the following three-letter abbreviations for the months

January	JAN
February	FEB
March	MAR
April	APR
May	MAY
June	JUN
July	JUL
August	AUG
September	SEP
October	OCT
November	NOV
December	DEC

e.g.

0	1	J	A	N	9	9
Day		Month			Year	

 = 1st January 1999

TIME

Unless specified otherwise, please use the 24 hour clock

e.g.

1	5	3	0
24hr:min			

 = 3.30 p.m

PATIENT INITIALS

Please use the following format:

e.g. XXXXXXXXXX

ROUTE KEY FOR PRIOR/CONCOMITANT MEDICATION PAGE

PO = By mouth	SL = Sublingual	TD = Transdermal
IV = Intravenous	IT = Intrathecal	IH = Inhaled
IM = Intramuscular	VA = Vaginal	SC = Subcutaneous
IAR = Intra-arterial	NA = Nasal	PR = Rectal
TO = Topical	IA = Intra-articular injection	ID = Intradermal

**SUMMARY CHART OF STUDY PROCEDURES (OPEN BOXES)
PROTOCOL SB 207499/040**

Mark open boxes to confirm that each procedure has been completed.

Procedures	Visit 11	Visit 12
	Week 32	Week 36
Signed written informed consent		
Study Medication compliance		
Concomitant Medication		
Diary Card Review ⁷		
Adverse Experiences ⁸		
COPD Exacerbation assessment/Healthcare Ut.		
Physical (Including Respiratory) Examination		
Resting 12-Lead ECG		
Vital Signs (BP, HR) ³		
Overall Breathlessness (Modified Borg)		
Exercise Tolerance Test - 6 Minute Walk		
Post Exercise Breathlessness		
Pulmonary Function Tests ⁴		
Laboratory Tests ⁵		
Pregnancy Test ⁶		
Quality of Life Assessment: SGRQ		
Quality of Life Assessment: SF-36		
Dispense or re-dispense Open-Label Medication		
Study Continuation / Withdrawal		

³ *Orthostatic blood pressure and heart rate are measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal.*

⁴ *To include FEV₁, FEV₆, FVC, FEF₂₅₋₇₅, FEF₇₅, and PEFR.*

⁵ *Faecal occult blood is measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal. Baseline measure is taken from last FOB in Study 042 or Study 091*

⁶ *Serum pregnancy test for female patients of child bearing potential. Urine test only is done at Follow-Up Visit.*

⁷ *A Diary Card is issued at each visit. The patient will use the Diary Card to record if they feel differently since the previous visit.*

⁸ *Patients will be assessed for GI AEs at every visit.*



Protocol	Centre Number	Patient Number	Patient Initials		
207499/040		0 0 0 0 0			

MODULE 13

Please do not split modules

Module 13 : Visit 11 (Week 32) and Visit 12 (Week 36), Adverse Experiences, Conmeds, Medical Procedures, COPD Exacerbations, Resource Utilisation, Continuation/Withdrawal

CRF Pages 195 - 236

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

None

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 	Visit Date			Visit 11 Week 32
				Day 	Month 	Year 	

PRESENTATION TO CLINIC

Record time of presentation to clinic

24hr:min

Note: Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.

Record the date and time of the patient's last dose of short-acting beta₂ agonist

Day Month Yr 24hr:min
Record the date and time of the patient's last dose of long-acting beta₂ agonist

Day Month Yr 24hr:min

Record the date and time of the patient's last dose of anticholinergic

Day Month Yr 24hr:min

Has the patient smoked within the past 2 hours?

☐ No☐ Yes → If 'Yes' please record time

24hr:min
COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	 Day Month Yr	 Day Month Yr	 Day Month Yr	 Day Month Yr
Level of exacerbation (maximum intensity)	☐ Level 1	☐ Level 1	☐ Level 1	☐ Level 1
	☐ Level 2	☐ Level 2	☐ Level 2	☐ Level 2
	☐ Level 3	☐ Level 3	☐ Level 3	☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 11 Week 32

RESOURCE UTILISATION FOR EXACERBATIONS

If the patient has received any COPD exacerbation related medical care since the previous visit, please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

*Review the diary card for illegible/incomplete entries **in the presence of the patient***

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there had been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD Exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 11 Week 32

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	

Date and time of last dose of study medication prior to the study visit

[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70	[][]	[][]	[][]	[][]	[][][]

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance $\geq 80\%$ and $\leq 120\%$?

☐ No →

If 'No' please check the % compliance at the previous visit. If compliance was not $\geq 80\%$ and $\leq 120\%$ at the last visit, please withdraw the patient. Please complete the assessments for Visit 11 and the assessments for patients withdrawing or stopping the study at Visit 11, contained at the end of this visit.

☐ Yes

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 11 Week 32

SMOKING STATUS

Does the patient currently smoke?

☐ No☐ Yes → If 'Yes' please record the average number of cigarettes per day : [][]**PULMONARY REHABILITATION PROGRAMME**

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit?

☐ No☐ Yes**LABORATORY TESTS**

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential). Please refer to the instructions on the SBCL shipping form and manual.

Blood Sample Date

[][]	[][]	[][]
Day	Month	Yr

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below

Attach label here

Are there any **clinically significant worsenings** since the previous visit?☐ No☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module

Place the SBCL laboratory report in the plastic wallet at the back of this module

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Page	199

Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][][]		Visit 11 Week 32

URINALYSIS

Please perform urinalysis using the dipstick provided by SBCL and record the results in the patient notes.

Urine Sample Date

[][]	[][]	[][]
Day	Month	Yr

Are the dipstick results negative?

☐ No →

If 'No' please send the sample to SBCL for microscopy

☐ Yes
Are there any **clinically significant worsenings** since the previous visit on the SBCL report?
☐ No

☐ Yes →

If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

PREGNANCY TEST

Is the patient a female of child-bearing potential?

☐ No

☐ Yes →

If 'Yes' please request a pregnancy test on the SBCL requisition form.

Is the patient pregnant?

☐ No

☐ Yes →

If 'Yes' please withdraw the patient from the study, enter details in the Adverse Experience section. Complete the Early Withdrawal Visit (found in a separate book).

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Protocol		Patient Number	Patient Initials		Visit 11 Week 32
207499/040		0 0 0 0 0			

OVERALL BREATHLESSNESS ASSESSMENT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 11 Week 32

INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed: [][] / [][] / [][]
Day Month Yr

Were any clinically significant changes noted since the last visit?

☐ No

☐ Yes →

☐ Improvement

☐ Worsening →

Enter details in the Adverse Experience section at the back of this module.

Place the ECG trace in the plastic wallet at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 11 Week 32

PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and/or anticholinergic medications and/or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

STUDY MEDICATION LABEL

Issue the patient one bottle of open-label study medication (70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

**Attach study medication
label here**

Give the patient the first dose of study medication with food and record the date and time of administration below.

Date and time of administration

[][]	[][]	[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:	min	

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 11 Week 32

INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐

No →

If 'No' please complete the assessments for Visit 11 and the Assessments for Patients Withdrawing or Stopping the Study at Visit 11 contained on the following pages. Complete and fax the Withdrawal Form contained in the Withdrawal and Follow-Up Book.

☐

Yes →

If 'Yes' please:

- *Issue a new diary card. Remind the patient to record if they feel differently since starting the study*
- *Ask the patient to return for the next visit in 28 + / - 6 days.*
- **Remind the patient:**
 - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*
 - ii **not** *to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*
 - iii *to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonists (long-acting) for **12 hours** before the next visit.*
 - iv *to refrain from smoking for **2 hours** immediately preceding the visit.*
 - v *to bring back at the next visit any remaining study medication or study medication containers and the diary card.*
 - vi *to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.*

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 11 Week 32

ASSESSMENTS FOR PATIENTS WITHDRAWING OR STOPPING THE STUDY

Complete the assessments below only for patients who are withdrawing early from the study or stopping the study because the product has been registered or because the sponsor has terminated the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes →

If 'Yes' record details in the Adverse Experience section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 11 Week 32

FAECAL OCCULT BLOOD TEST

Issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-Up Visit.

VITAL SIGNS - ORTHOSTATIC CHANGE**1st Measurement: after 5 Minutes Supine**

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

Are there any clinically significant worsenings since the previous assessment?

☐ No

☐ Yes → If 'Yes' record details in the Adverse Experience section at the back of this module.

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Follow-Up Visit in 7 +/- 3 days.

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Protocol	Centre Number	Patient Number	Patient Initials	Visit Date	Visit 12 Week 36
207499/040		0 0 0 0 0		Day Month Year	

PRESENTATION TO CLINIC

Record time of presentation to clinic

 24hr:min

Note: *Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.*

Record the date and time of the patient's last dose of short-acting beta₂ agonist

Day	Month	Yr	24hr:min		

Record the date and time of the patient's last dose of long-acting beta₂ agonist

Day	Month	Yr	24hr:min		

Record the date and time of the patient's last dose of anticholinergic

Day	Month	Yr	24hr:min		

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes → If 'Yes' please record time

 24hr:min

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 12 Week 36

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of exacerbation (maximum intensity)	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.

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Protocol		Patient Number	Patient Initials		Visit 12 Week 36
207499/040		0 0 0 0 0			

RESOURCE UTILISATION FOR COPD EXACERBATIONS

Please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

Review the diary card for illegible/incomplete entries **in the presence of the patient**

ADVERSE EXPERIENCES

Please complete the Adverse Experience section at the back of this module. If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

Please complete the Concomitant Medication section at the back of this module. If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD Exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 12 Week 36

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	

Date and time of last dose of study medication prior to the study visit

[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70	[][]	[][]	[][]	[][]	[][][][]

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance $\geq 80\%$ and $\leq 120\%$?

☐ No →

If 'No' please check the % compliance at the previous visit. If compliance was not $\geq 80\%$ and $\leq 120\%$ at the last visit, please withdraw the patient. Please complete the assessments for Visit 12 and the assessments for patients withdrawing or stopping the study at Visit 12, contained at the end of this visit.

☐ Yes

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Page	210

Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 12 Week 36

SMOKING STATUS

Does the patient currently smoke?

☐ No☐ Yes → If 'Yes' please record the average number of cigarettes per day : [][]**PULMONARY REHABILITATION PROGRAMME**

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit?

☐ No☐ Yes**LABORATORY TESTS**

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential). Please refer to the instructions on the SBCL shipping form and manual.

Blood Sample Date

[][]	[][]	[][]
Day	Month	Yr

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below

Attach label here

Are there any **clinically significant worsenings** since the previous visit?☐ No☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module

Place the SBCL laboratory report in the plastic wallet at the back of this module

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URINALYSIS

Please perform urinalysis using the dipstick provided by SBCL and record the results in the patient notes.

Urine Sample Date [][][][][][]
 Day Month Yr

Are the dipstick results negative?

- ☐ No → *If 'No' please send the sample to SBCL for microscopy*
- ☐ Yes

Are there any **clinically significant worsenings** since the previous visit on the SBCL report?

- ☐ No
- ☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

PREGNANCY TEST

Is the patient a female of child-bearing potential?

- ☐ No
- ☐ Yes → *If 'Yes' please request a pregnancy test on the SBCL requisition form.*

Is the patient pregnant?

- ☐ No
- ☐ Yes → *If 'Yes' please withdraw the patient from the study, enter details in the Adverse Experience section. Complete the Early Withdrawal Visit (found in a separate book).*

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OVERALL BREATHLESSNESS ASSESSMENT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed: [][] / [][] / [][]
Day Month Yr

Were any clinically significant changes noted since the last visit?

☐ No

☐ Yes → ☐ Improvement

☐ Worsening →

Enter details in the Adverse Experience section at the back of this module.

Place the ECG trace in the plastic wallet at the back of this module.

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EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes. If the patient was too ill to attempt the test, please mark the 'Yes' box and enter 0 for distance walked.

☐ No

☐ Yes → If 'Yes', Distance walked Metres

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

POST-EXERCISE BREATHLESSNESS (Immediately after the patient completes the exercise tolerance)
Heart Rate beats/min
Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

- 0 Nothing at all
- 1 Very, very slight (just noticeable)
- 2 Very slight
- 3 Moderate
- 4 Somewhat severe
- 5 Severe
- 6
- 7 Very severe
- 8
- 9 Very, very severe (almost maximal)
- 10 Maximal

Overall breathlessness score .
INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise tolerance test (rest for at least 10 minutes) before performing the pulmonary function tests.

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PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and/or anticholinergic medications and/or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

STUDY MEDICATION LABEL

Issue the patient one bottle of open-label study medication (70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

Attach study medication
label here

Give the patient the first dose of study medication with food and record the date and time of administration below.

Date and time of administration

Day	Month	Yr	24hr:	min			

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INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐ No →

If 'No' please complete the assessments for Visit 12 and the Assessments for Patients Withdrawing or Stopping the Study at Visit 12 contained on the following pages. Complete and fax the Withdrawal Form contained in the Withdrawal and Follow-Up Book.

☐ Yes →

If 'Yes' please:

- *Issue a new diary card. Remind the patient to record if they feel differently since starting the study*
- *Ask the patient to return for the next visit in 28 +/- 6 days.*
- *Complete the Study Continuation / Withdrawal page at the back of this module.*
- **Remind the patient:**
 - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*
 - ii **not** *to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*
 - iii *to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonists (long-acting) for **12 hours** before the next visit.*
 - iv *to refrain from smoking for **2 hours** immediately preceding the visit.*
 - v *to bring back at the next visit any remaining study medication or study medication containers and the diary card.*
 - vi *to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.*

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ASSESSMENTS FOR PATIENTS WITHDRAWING OR STOPPING THE STUDY

Complete the assessments below only for patients who are withdrawing early from the study or stopping the study because the product has been registered or because the sponsor has terminated the study.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a clinically significant worsening in the patient's physical condition since the previous examination?

☐ No

☐ Yes →

If 'Yes' record details in the Adverse Experience section at the back of this module.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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FAECAL OCCULT BLOOD TEST

Issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-Up Visit.

VITAL SIGNS - ORTHOSTATIC CHANGE**1st Measurement: after 5 Minutes Supine**

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

Are there any clinically significant worsenings since the previous assessment?

☐ No

☐ Yes → If 'Yes' record details in the Adverse Experience section at the back of this module.

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Follow-Up Visit in 7 +/- 3 days.

ADVERSE EXPERIENCES (Non-serious)**DEFINITIONS****INTENSITY (Maximum)**

MILD	<i>Adverse experience which is easily tolerated</i>
MODERATE	<i>Adverse experience sufficiently discomforting to interfere with daily activities</i>
SEVERE	<i>Adverse experience which prevents normal everyday activities</i>

RELATIONSHIP TO INVESTIGATIONAL DRUG

NOT RELATED	<i>The adverse experience is definitely not related to the test drug</i>
UNLIKELY	<i>There are other more likely causes and the drug is not suspected as a cause</i>
SUSPECTED (REASONABLE POSSIBILITY)	<i>A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug</i>
PROBABLE	<i>There probably is a direct cause and effect relationship between the adverse experience and the study drug</i>

SERIOUS ADVERSE EXPERIENCE (SAE)

An SAE is any event which is :-

- 1 - fatal
- 2 - life threatening
- 3 - disabling/incapacitating
- 4 - results in hospitalisation (excluding elective surgery or routine clinical procedures)
- 5 - prolongs a hospital stay
- 6 - associated with congenital abnormality
- 7 - cancer
- 8 - associated with overdose
- 9 - In addition any event which the investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the study procedures should be reported as a serious event

IF AN SAE OCCURS, PLEASE GO TO SAE SECTION IMMEDIATELY AND FOLLOW THE INSTRUCTIONS GIVEN THERE

Use each form for a maximum of two experiences

PLEASE REMEMBER ALL QUESTIONS ON ADVERSE EXPERIENCES FORM SHOULD BE COMPLETED



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ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous module?" Provide the diagnosis, **not** symptoms, where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbations section

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no adverse experiences occurred since the previous module, please mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	



Protocol		Patient Number	Patient Initials		
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ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous module?" Provide the diagnosis, **not** symptoms, where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbations section

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no further adverse experiences or changes in adverse experiences occurred since the previous module, please mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date :	 Day Month Yr



Protocol		Patient Number	Patient Initials		
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ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous module?" Provide the diagnosis, **not** symptoms, where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbations section

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no further adverse experiences or changes in adverse experiences occurred since the previous module, please mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date :	 Day Month Yr



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CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the previous module.
(Please write using BLOCK CAPITALS).

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

☐ No concomitant medication changes since the previous module

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded on the Adverse Experience Form using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the new start and end date.

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)			
					Day	Mth	Yr	Day	Mth	Yr	
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* For Route, see tab for acceptable abbreviations.



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CONCOMITANT MEDICATION - Continued

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded on the Adverse Experience Form using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the new start and end date.

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)			
					Day	Mth	Yr	Day	Mth	Yr	
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* For Route, see tab for acceptable abbreviations.



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MEDICAL PROCEDURES - (Excluding treatment for COPD Exacerbations)

Do not record procedures used to treat COPD exacerbations here, record them in the COPD Exacerbation section.

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed since the previous module?

☐ No

☐ Yes → If 'Yes', please record details below using standard medical terminology (Please print clearly)

All indications for procedures should be recorded in the Adverse Experience section

Procedure	Indication	Procedure Start Date			Procedure End Date		
		Day	Mth	Yr	Day	Mth	Yr
For SB							
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DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.
All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages**

If no COPD Exacerbations since the previous module mark this box. ☐

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____ Date : Day Month Yr		



Protocol		Patient Number	Patient Initials		
207499/040		0 0 0 0 0			

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.

All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages**

If no further COPD exacerbations or changes to COPD exacerbations have occurred since the previous module, mark this box. ☐

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
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Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	



Protocol		Patient Number	Patient Initials		
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DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.

All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages**

If no further COPD exacerbations or changes to COPD exacerbations have occurred since the previous module, mark this box. ☐

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)**SAEs MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS****COMPLETE THE SAE PAGES OPPOSITE**

Please complete these pages as fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Experience Course' blank and update it later

SIGN AND DATE THE SAE PAGE**PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE**

- Demography
- Significant Medical/Surgical History and Physical Examination
- Study Medication Record
- Concomitant Medication
- Form D (if applicable)

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE
(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO:

Your local SB CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local SB CRA/Medical monitor within 24 hours



Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date		
				Day	Month	Year
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Person Reporting SAE _____ (Please print clearly)		AEGIS Number _____
Serious Adverse Experience (Please print clearly)	COPD Exacerbation	→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time _____ Day Month Yr 24hr:min		
End Date and Time (If ongoing please leave blank) _____ Day Month Yr 24hr:min		
Outcome If patient died, please complete Form D	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes _____ ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) Please specify _____
Corrective Therapy If 'Yes', record details in the COPD Medication or Procedures section	☐ Yes ☐ No	☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	☐ Another drug Please specify _____



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Protocol 207499/040	Centre Number [][][]	Patient Number 0 0 0 0 0	Patient Initials [][][]	SB Receipt Date Day Month Year [][][][][][]

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)**Relevant Laboratory Data**

Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	[][][][][][] Day Month Yr			
	[][][][][][] Day Month Yr			
	[][][][][][] Day Month Yr			
	[][][][][][] Day Month Yr			

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

[][][][][][]

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

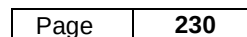
[][][]	[][][]	[][][]
Day	Month	Year

Please PRINT Name**SB Medical Monitor's Signature:**

Date

Please PRINT Name

[][][]	[][][]	[][][]
Day	Month	Year



Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date		
				Day	Month	Year
207499/040		0 0 0 0 0				

Person Reporting SAE _____ (Please print clearly)		AEGIS Number _____
Serious Adverse Experience (Please print clearly)	COPD Exacerbation	→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time _____ Day Month Yr 24hr:min		
End Date and Time (If ongoing please leave blank) _____ Day Month Yr 24hr:min		
Outcome If patient died, please complete Form D	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes _____ ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) Please specify _____
Corrective Therapy If 'Yes', record details in the COPD Medication or Procedures section	☐ Yes ☐ No	☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	☐ Another drug Please specify _____



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Protocol 207499/040	Centre Number <table border="1"><tr><td></td><td></td><td></td></tr></table>				Patient Number <table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>					SB Receipt Date Day Month Year <table border="1"><tr><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>						
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SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range						
	<table border="1"><tr><td></td><td></td><td></td></tr><tr><td>Day</td><td>Month</td><td>Yr</td></tr></table>				Day	Month	Yr			
Day	Month	Yr								
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Day	Month	Yr								
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Day	Month	Yr								

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?
☐ No ☐ Yes

Randomisation / Study Medication Number:

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

Day	Month	Year

Please PRINT Name



Protocol 207499/040	Centre Number <table border="1"><tr><td></td><td></td><td></td></tr></table>				Patient Number <table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						
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MEDICATION FOR COPD EXACERBATIONS

Has the patient taken any medication for COPD exacerbations since the previous module?

☐ No☐ Yes → If 'Yes', please record details below

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)			
					Day	Mth	Yr	Day	Mth	Yr	
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
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				COPD EXACERBATION							☐
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				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											

* For Route, see tab for acceptable abbreviations.



Protocol		Patient Number	Patient Initials		
207499/040		0 0 0 0 0			

MEDICAL PROCEDURES

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since the previous module?

☐ No

☐ Yes → If 'Yes', please record details below using standard medical terminology

Procedure	Indication	Procedure Start Date			Procedure End Date		
		Day	Mth	Yr	Day	Mth	Yr
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
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	COPD EXACERBATION						
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Protocol 207499/040	Centre Number <table border="1"><tr><td></td><td></td><td></td></tr></table>				Patient Number <table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						
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HEALTHCARE RESOURCE UTILISATION FOR COPD EXACERBATIONS

Complete this form for any COPD exacerbation related medical care the patient received since the previous module

Physician Visits (i.e., COPD care excluding scheduled protocol visits)

☐ There were no physician visits since the previous module

Date of Visit Day Mth Yr	Reason for Visit						
<table border="1"><tr><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>							
<table border="1"><tr><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>							
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Emergency Room (ER)/Urgent Care Visits/Casualty Department Procedures (i.e., lung surgery)

☐ There were no Emergency Room/Urgent Care Visits/Casualty Department Procedures since previous module

Date of Visit Day Mth Yr	Reason for Visit	Patient Admitted from ER?							
		Yes	No						
<table border="1"><tr><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>								☐	☐
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Protocol 207499/040	Centre Number <table border="1"><tr><td></td><td></td><td></td></tr></table>				Patient Number <table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						
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HEALTHCARE RESOURCE UTILISATION FOR COPD EXACERBATIONS - (cont)

Hospitalisations (also record details of any hospitalisation in the Serious Adverse Experience - COPD Exacerbation section)

☐ There were no hospitalisations since the previous module

Date of Admission Day Mth Yr	Date of Discharge Day Mth Yr	Reason for Admission										
<table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>						<table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>						
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Intensive Care Unit (ICU) stays (did the patient stay in the ICU during any of the above hospitalisations?)

☐ There were no ICU stays since previous module

Date Admitted to ICU Day Mth Yr	Date Discharged from ICU Day Mth Yr	Reason for ICU Admission										
<table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>						<table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>						
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Lost Work Days (i.e., days patient missed work due to COPD excluding scheduled protocol visits)

☐ There were no lost work days since the previous module

Stop Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence										
<table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>						<table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>						
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Protocol 207499/040	Centre Number <table border="1"> <tr> <td></td><td></td><td></td> </tr> </table>				Patient Number <table border="1"> <tr> <td>0</td><td>0</td><td>0</td><td>0</td><td>0</td> </tr> </table>	0	0	0	0	0	Patient Initials <table border="1"> <tr> <td></td><td></td><td></td><td></td> </tr> </table>						
0	0	0	0	0													

STUDY CONCLUSION/WITHDRAWAL

Is the patient continuing in the study?

☐ Yes

☐ No →

*If 'No' please mark the **primary** cause of withdrawal and enter the date of the final visit and the date of the final dose*

[1] ☐ Adverse experience (complete AE or SAE section)

[2] ☐ Insufficient therapeutic effect

[3] ☐ Protocol deviation (including non-compliance)

[4] ☐ Lost to follow-up

[7] ☐ Other - specify: _____

Date of Final Visit

Day	Month	Yr	

Date of Final dose

Day	Month	Yr	

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data on this case report form and that all information is complete and accurate.

Investigator's Signature _____

Date

Day	Month	Yr	

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)

SAEs MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS

COMPLETE THE SAE PAGES OPPOSITE

Please complete these pages as fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Experience Course' blank and update it later

SIGN AND DATE THE SAE PAGE**PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE**

- Demography
- Significant Medical/Surgical History and Physical Examination
- Study Medication Record
- Medical Procedures
- Concomitant Medication
- Form D (if applicable)

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE

(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO:

Your local SB CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local SB CRA/Medical monitor within 24 hours



Protocol	Centre Number	Patient Number	Patient Initials		
207499/040		0 0 0 0 0			

MOD14 & MOD15 - SERIOUS ADVERSE EXPERIENCES

MOD14 & MOD15	Serious Adverse Experiences
MOD14 :	237, 238
MOD15	239, 240

Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date		
				Day	Month	Year
207499/040		0 0 0 0 0				

[illegible]



Protocol 207499/040	Centre Number [][][]	Patient Number 0 0 0 0 0	Patient Initials [][][][]	SB Receipt Date Day Month Year [][][][][][]

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data**

Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

[][][][][]

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

[][][]	[][][]	[][][]
Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

[][][]	[][][]	[][][]
Day	Month	Year

Please PRINT Name

Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date		
				Day	Month	Year
207499/040		0 0 0 0 0				

[illegible]



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Protocol 207499/040	Centre Number <table border="1"><tr><td></td><td></td><td></td></tr></table>				Patient Number <table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>					SB Receipt Date Day Month Year <table border="1"><tr><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>						
0	0	0	0	0																		

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range						
	<table border="1"><tr><td></td><td></td><td></td></tr><tr><td>Day</td><td>Month</td><td>Yr</td></tr></table>				Day	Month	Yr			
Day	Month	Yr								
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Day	Month	Yr								

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

Day	Month	Year

Please PRINT Name

Protocol	Centre Number	Patient Number	Patient Initials
207499/040		0 0 0 0 0	

CONFIDENTIAL*PROTOCOL 207499/040**BOOK 6 : VISITS 13 AND 14 (WEEKS 40 AND 44)*

***A MULTICENTRE, OPEN-LABEL EXTENSION STUDY TO EVALUATE
THE SAFETY, TOLERABILITY AND EFFICACY OF ORAL SB 207499
(15mg TWICE DAILY) IN PATIENTS WITH CHRONIC OBSTRUCTIVE
PULMONARY DISEASE (COPD)***

GENERAL INSTRUCTIONS

- Write clearly in capital letters using a black ball point pen and press firmly so that all copies are legible
- Do not write in shaded areas
- Answer ALL questions on every page
- Enter "N/A" if information requested is not available
- Initial and date all changes, additions or deletions. Use a single pen stroke to remove an incorrect entry
- Enter the patient initials on all pages on which information has been entered and the patient number and centre number where required

Do not enter additional data/information after the set of CRF pages has been split/separated

The cover flap or plastic writing board should be used to divide each set of pages before writing on them with a ball point pen

DATE

Please use the following three-letter abbreviations for the months

January	JAN
February	FEB
March	MAR
April	APR
May	MAY
June	JUN
July	JUL
August	AUG
September	SEP
October	OCT
November	NOV
December	DEC

e.g.

0	1	J	A	N	9	9
Day		Month			Year	

 = 1st January 1999

TIME

Unless specified otherwise, please use the 24 hour clock

e.g.

1	5	3	0
24hr:min			

 = 3.30 p.m

PATIENT INITIALS

Please use the following format:

e.g. XXXXXXXXXX

ROUTE KEY FOR PRIOR/CONCOMITANT MEDICATION PAGE

PO = By mouth	SL = Sublingual	TD = Transdermal
IV = Intravenous	IT = Intrathecal	IH = Inhaled
IM = Intramuscular	VA = Vaginal	SC = Subcutaneous
IAR = Intra-arterial	NA = Nasal	PR = Rectal
TO = Topical	IA = Intra-articular injection	ID = Intradermal

SUMMARY CHART OF STUDY PROCEDURES (OPEN BOXES)
PROTOCOL SB 207499/040

Mark open boxes to confirm that each procedure has been completed.

Procedures	Visit 13 Week 40	Visit 14 Week 44
Signed written informed consent		
Study Medication compliance		
Concomitant Medication		
Diary Card Review ⁷		
Adverse Experiences ⁸		
COPD Exacerbation assessment/Healthcare Ut.		
Physical (Including Respiratory) Examination		
Resting 12-Lead ECG		
Vital Signs (BP, HR) ³		
Overall Breathlessness (Modified Borg)		
Exercise Tolerance Test - 6 Minute Walk		
Post Exercise Breathlessness		
Pulmonary Function Tests ⁴		
Laboratory Tests ⁵		
Pregnancy Test ⁶		
Quality of Life Assessment: SGRQ		
Quality of Life Assessment: SF-36		
Dispense or re-dispense Open-Label Medication		
Study Continuation / Withdrawal		

³ *Orthostatic blood pressure and heart rate are measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal.*

⁴ *To include FEV₁, FEV₆, FVC, FEF₂₅₋₇₅, FEF₇₅, and PEFR.*

⁵ *Faecal occult blood is measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal. Baseline measure is taken from last FOB in Study 042 or Study 091*

⁶ *Serum pregnancy test for female patients of child bearing potential. Urine test only is done at Follow-Up Visit.*

⁷ *A Diary Card is issued at each visit. The patient will use the Diary Card to record if they feel different since the previous visit.*

⁸ *Patients will be assessed for GI AEs at every visit.*

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Protocol	Centre Number	Patient Number	Patient Initials		
207499/040					

MODULE 16

Please do not split modules

Module 16 : Visit 13 (Week 40) and Visit 14 (Week 44), Adverse Experiences, Conmeds, Medical Procedures, COPD Exacerbations, Resource Utilisation, Continuation/Withdrawal

CRF Pages 241 - 280

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

None

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Protocol 207499/040	Centre Number	Patient Number	Patient Initials	Visit Date			Visit 13 Week 40
				Day	Month	Year	
		0 0 0 0 0					

PRESENTATION TO CLINIC

Record time of presentation to clinic

 24hr:min

Note: Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.

Record the date and time of the patient's last dose of short-acting beta₂ agonist

Day	Month	Yr			

 24hr:min
Record the date and time of the patient's last dose of long-acting beta₂ agonist

Day	Month	Yr			

 24hr:min

Record the date and time of the patient's last dose of anticholinergic

Day	Month	Yr			

 24hr:min

Has the patient smoked within the past 2 hours?

☐ No☐ Yes → If 'Yes' please record time

 24hr:min
COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	<table border="1"> <tr> <td></td> <td></td> <td></td> </tr> <tr> <td>Day</td> <td>Month</td> <td>Yr</td> </tr> </table>				Day	Month	Yr	<table border="1"> <tr> <td></td> <td></td> <td></td> </tr> <tr> <td>Day</td> <td>Month</td> <td>Yr</td> </tr> </table>				Day	Month	Yr	<table border="1"> <tr> <td></td> <td></td> <td></td> </tr> <tr> <td>Day</td> <td>Month</td> <td>Yr</td> </tr> </table>				Day	Month	Yr	<table border="1"> <tr> <td></td> <td></td> <td></td> </tr> <tr> <td>Day</td> <td>Month</td> <td>Yr</td> </tr> </table>				Day	Month	Yr
Day	Month	Yr																										
Day	Month	Yr																										
Day	Month	Yr																										
Day	Month	Yr																										
Level of exacerbation (maximum intensity)	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3																								

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 13 Week 40

RESOURCE UTILISATION FOR EXACERBATIONS

If the patient has received any COPD exacerbation related medical care since the previous visit, please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

*Review the diary card for illegible/incomplete entries **in the presence of the patient***

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there had been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD Exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 13 Week 40

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	

Date and time of last dose of study medication prior to the study visit

[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70	[][]	[][]	[][]	[][]	[][][]

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance $\geq 80\%$ and $\leq 120\%$?

☐ No →

If 'No' please check the % compliance at the previous visit. If compliance was not $\geq 80\%$ and $\leq 120\%$ at the last visit, please withdraw the patient. Please complete the assessments for Visit 13 and the assessments for patients withdrawing or stopping the study at Visit 13, contained at the end of this visit.

☐ Yes

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 13 Week 40

SMOKING STATUS

Does the patient currently smoke?

☐ No☐ Yes → If 'Yes' please record the average number of cigarettes per day : [][]**PULMONARY REHABILITATION PROGRAMME**

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit?

☐ No☐ Yes**LABORATORY TESTS**

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential). Please refer to the instructions on the SBCL shipping form and manual.

Blood Sample Date

[][]	[][]	[][]
Day	Month	Yr

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below

Attach label here

Are there any **clinically significant worsenings** since the previous visit?☐ No☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module

Place the SBCL laboratory report in the plastic wallet at the back of this module

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][][]		Visit 13 Week 40

URINALYSIS

Please perform urinalysis using the dipstick provided by SBCL and record the results in the patient notes.

Urine Sample Date

Day	Month	Yr		

Are the dipstick results negative?

☐ No →

If 'No' please send the sample to SBCL for microscopy

☐ Yes

Are there any **clinically significant worsenings** since the previous visit on the SBCL report?

☐ No

☐ Yes →

If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

PREGNANCY TEST

Is the patient a female of child-bearing potential?

☐ No

☐ Yes →

If 'Yes' please request a pregnancy test on the SBCL requisition form.

Is the patient pregnant?

☐ No

☐ Yes →

If 'Yes' please withdraw the patient from the study, enter details in the Adverse Experience section. Complete the Early Withdrawal Visit (found in a separate book).

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Protocol		Patient Number	Patient Initials		Visit 13 Week 40
207499/040		0 0 0 0 0			

OVERALL BREATHLESSNESS ASSESSMENT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 13 Week 40

INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed: [][] / [][] / [][]
Day Month Yr

Were any clinically significant changes noted since the last visit?

☐ No

☐ Yes → ☐ Improvement

☐ Worsening →

Enter details in the Adverse Experience section at the back of this module.

Place the ECG trace in the plastic wallet at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 13 Week 40
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PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and/or anticholinergic medications and/or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

STUDY MEDICATION LABEL

Issue the patient one bottle of open-label study medication (70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

**Attach study medication
label here**

Give the patient the first dose of study medication with food and record the date and time of administration below.

Date and time of administration

Day	Month	Yr	24hr	:	min		

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 13 Week 40

INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐

No →

If 'No' please complete the assessments for Visit 13 and the Assessments for Patients Withdrawing or Stopping the Study at Visit 13 contained on the following pages. Complete and fax the Withdrawal Form contained in the Withdrawal and Follow-Up Book.

☐

Yes →

If 'Yes' please:

- *Issue a new diary card. Remind the patient to record if they feel differently since starting the study*
- *Ask the patient to return for the next visit in 28 + / - 6 days.*
- **Remind the patient:**
 - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*
 - ii ***not** to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*
 - iii *to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonists (long-acting) for **12 hours** before the next visit.*
 - iv *to refrain from smoking for **2 hours** immediately preceding the visit.*
 - v *to bring back at the next visit any remaining study medication or study medication containers and the diary card.*
 - vi *to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.*

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 13 Week 40

ASSESSMENTS FOR PATIENTS WITHDRAWING OR STOPPING THE STUDY

Complete the assessments below only for patients who are withdrawing early from the study or stopping the study because the product has been registered or because the sponsor has terminated the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes →

If 'Yes' record details in the Adverse Experience section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 13 Week 40

FAECAL OCCULT BLOOD TEST

Issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-Up Visit.

VITAL SIGNS - ORTHOSTATIC CHANGE**1st Measurement: After 5 Minutes Supine**

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

Are there any clinically significant worsenings since the previous assessment?

☐ No

☐ Yes → If 'Yes' record details in the Adverse Experience section at the back of this module.

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Follow-Up Visit in 7 +/- 3 days.

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Protocol 207499/040	Centre Number	Patient Number	Patient Initials	Visit Date			Visit 14 Week 44
				Day	Month	Year	
		0 0 0 0 0					

PRESENTATION TO CLINIC

Record time of presentation to clinic

 24hr:min

Note: Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.

Record the date and time of the patient's last dose of short-acting beta₂ agonist

Day	Month	Yr			

 24hr:min
Record the date and time of the patient's last dose of long-acting beta₂ agonist

Day	Month	Yr			

 24hr:min

Record the date and time of the patient's last dose of anticholinergic

Day	Month	Yr			

 24hr:min

Has the patient smoked within the past 2 hours?

☐ No☐ Yes → If 'Yes' please record time

 24hr:min
COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	<table border="1"> <tr> <td></td> <td></td> <td></td> </tr> <tr> <td>Day</td> <td>Month</td> <td>Yr</td> </tr> </table>				Day	Month	Yr	<table border="1"> <tr> <td></td> <td></td> <td></td> </tr> <tr> <td>Day</td> <td>Month</td> <td>Yr</td> </tr> </table>				Day	Month	Yr	<table border="1"> <tr> <td></td> <td></td> <td></td> </tr> <tr> <td>Day</td> <td>Month</td> <td>Yr</td> </tr> </table>				Day	Month	Yr	<table border="1"> <tr> <td></td> <td></td> <td></td> </tr> <tr> <td>Day</td> <td>Month</td> <td>Yr</td> </tr> </table>				Day	Month	Yr
Day	Month	Yr																										
Day	Month	Yr																										
Day	Month	Yr																										
Day	Month	Yr																										
Level of exacerbation (maximum intensity)	☐ Level 1	☐ Level 1	☐ Level 1	☐ Level 1																								
	☐ Level 2	☐ Level 2	☐ Level 2	☐ Level 2																								
	☐ Level 3	☐ Level 3	☐ Level 3	☐ Level 3																								

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.

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RESOURCE UTILISATION FOR COPD EXACERBATIONS

Please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

Review the diary card for illegible/incomplete entries **in the presence of the patient**

ADVERSE EXPERIENCES

Please complete the Adverse Experience section at the back of this module. If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

Please complete the Concomitant Medication section at the back of this module. If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD Exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 14 Week 44

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)
[][][][][][]	[][][][][][]	[]	
[][][][][][]	[][][][][][]	[]	
[][][][][][]	[][][][][][]	[]	

Date and time of last dose of study medication prior to the study visit

[][]	[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:	min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70	[][]	[][]	[][]	[][]	[][][][]

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance $\geq 80\%$ and $\leq 120\%$?

☐ No →

If 'No' please check the % compliance at the previous visit. If compliance was not $\geq 80\%$ and $\leq 120\%$ at the last visit, please withdraw the patient. Please complete the assessments for Visit 14 and the assessments for patients withdrawing or stopping the study at Visit 14, contained at the end of this visit.

☐ Yes

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 14 Week 44

SMOKING STATUS

Does the patient currently smoke?

☐ No☐ Yes → If 'Yes' please record the average number of cigarettes per day : [][]**PULMONARY REHABILITATION PROGRAMME**

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit?

☐ No☐ Yes**LABORATORY TESTS**

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential). Please refer to the instructions on the SBCL shipping form and manual.

Blood Sample Date

[][]	[][]	[][]
Day	Month	Yr

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below

Attach label here

Are there any **clinically significant worsenings** since the previous visit?☐ No☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module

Place the SBCL laboratory report in the plastic wallet at the back of this module

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][][]		Visit 14 Week 44

URINALYSIS

Please perform urinalysis using the dipstick provided by SBCL and record the results in the patient notes.

Urine Sample Date [][][][][][]
 Day Month Yr

Are the dipstick results negative?

- ☐ No → *If 'No' please send the sample to SBCL for microscopy*
- ☐ Yes

Are there any **clinically significant worsenings** since the previous visit on the SBCL report?

- ☐ No
- ☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

PREGNANCY TEST

Is the patient a female of child-bearing potential?

- ☐ No
- ☐ Yes → *If 'Yes' please request a pregnancy test on the SBCL requisition form.*

Is the patient pregnant?

- ☐ No
- ☐ Yes → *If 'Yes' please withdraw the patient from the study, enter details in the Adverse Experience section. Complete the Early Withdrawal Visit (found in a separate book).*

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Protocol		Patient Number	Patient Initials		Visit 14 Week 44
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OVERALL BREATHLESSNESS ASSESSMENT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 14 Week 44

INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed: [][] / [][] / [][]
Day Month Yr

Were any clinically significant changes noted since the last visit?

☐ No

☐ Yes →

☐ Improvement

☐ Worsening →

Enter details in the Adverse Experience section at the back of this module.

Place the ECG trace in the plastic wallet at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 14 Week 44
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PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and/or anticholinergic medications and/or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

STUDY MEDICATION LABEL

Issue the patient one bottle of open-label study medication (70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

Attach study medication
label here

Give the patient the first dose of study medication with food and record the date and time of administration below.

Date and time of administration

Day	Month	Yr	24hr:	min			

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][][]		Visit 14 Week 44

INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐ No →

If 'No' please complete the assessments for Visit 14 and the Assessments for Patients Withdrawing or Stopping the Study at Visit 14 contained on the following pages. Complete and fax the Withdrawal Form contained in the Withdrawal and Follow-Up Book.

☐ Yes →

If 'Yes' please:

- *Issue a new diary card. Remind the patient to record if they feel differently since starting the study*
- *Ask the patient to return for the next visit in 28 +/- 6 days.*
- *Complete the Study Continuation / Withdrawal page at the back of this module.*
- **Remind the patient:**
 - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*
 - ii **not** *to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*
 - iii *to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonists (long-acting) for **12 hours** before the next visit.*
 - iv *to refrain from smoking for **2 hours** immediately preceding the visit.*
 - v *to bring back at the next visit any remaining study medication or study medication containers and the diary card.*
 - vi *to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.*

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 14 Week 44

ASSESSMENTS FOR PATIENTS WITHDRAWING OR STOPPING THE STUDY

Complete the assessments below only for patients who are withdrawing early from the study or stopping the study because the product has been registered or because the sponsor has terminated the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a clinically significant worsening in the patient's physical condition since the previous examination?

☐ No

☐ Yes →

If 'Yes' record details in the Adverse Experience section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 14 Week 44

FAECAL OCCULT BLOOD TEST

Issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-Up Visit.

VITAL SIGNS - ORTHOSTATIC CHANGE**1st Measurement: After 5 Minutes Supine**

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

Are there any clinically significant worsenings since the previous assessment?

☐ No

☐ Yes → If 'Yes' record details in the Adverse Experience section at the back of this module.

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Follow-Up Visit in 7 +/- 3 days.

ADVERSE EXPERIENCES (Non-serious)**DEFINITIONS****INTENSITY (Maximum)**

MILD	<i>Adverse experience which is easily tolerated</i>
MODERATE	<i>Adverse experience sufficiently discomforting to interfere with daily activities</i>
SEVERE	<i>Adverse experience which prevents normal everyday activities</i>

RELATIONSHIP TO INVESTIGATIONAL DRUG

NOT RELATED	<i>The adverse experience is definitely not related to the test drug</i>
UNLIKELY	<i>There are other more likely causes and the drug is not suspected as a cause</i>
SUSPECTED (REASONABLE POSSIBILITY)	<i>A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug</i>
PROBABLE	<i>There probably is a direct cause and effect relationship between the adverse experience and the study drug</i>

SERIOUS ADVERSE EXPERIENCE (SAE)

An SAE is any event which is :-

- 1 - fatal
- 2 - life threatening
- 3 - disabling/incapacitating
- 4 - results in hospitalisation (excluding elective surgery or routine clinical procedures)
- 5 - prolongs a hospital stay
- 6 - associated with congenital abnormality
- 7 - cancer
- 8 - associated with overdose
- 9 - In addition any event which the investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the study procedures should be reported as a serious event

IF AN SAE OCCURS, PLEASE GO TO SAE SECTION IMMEDIATELY AND FOLLOW THE INSTRUCTIONS GIVEN THERE

Use each form for a maximum of two experiences

PLEASE REMEMBER ALL QUESTIONS ON ADVERSE EXPERIENCES FORM SHOULD BE COMPLETED

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Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous module?" Provide the diagnosis, **not** symptoms, where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbations section

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no adverse experiences occurred since the previous module, please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous module?" Provide the diagnosis, **not** symptoms, where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbations section

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no further adverse experiences or changes in adverse experiences occurred since the previous module, please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous module?" Provide the diagnosis, **not** symptoms, where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbations section

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no further adverse experiences or changes in adverse experiences occurred since the previous module, please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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Protocol	Centre Number	Patient Number	Patient Initials		
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CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the previous module.
(Please write using BLOCK CAPITALS).

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

☐ No concomitant medication changes since the previous module

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded on the Adverse Experience Form using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the new start and end date.

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)			
					Day	Mth	Yr	Day	Mth	Yr	
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* For Route, see tab for acceptable abbreviations.											

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CONCOMITANT MEDICATION - Continued

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded on the Adverse Experience Form using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the new start and end date.

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)			
					Day	Mth	Yr	Day	Mth	Yr	
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* For Route, see tab for acceptable abbreviations.

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Protocol	Centre Number	Patient Number	Patient Initials		
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MEDICAL PROCEDURES - (Excluding treatment for COPD Exacerbations)

Do not record procedures used to treat COPD exacerbations here, record them in the COPD Exacerbation section.

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed since the previous module?

☐ No

☐ Yes → If 'Yes', please record details below using standard medical terminology (Please print clearly)

All indications for procedures should be recorded in the Adverse Experience section

Procedure	Indication	Procedure Start Date			Procedure End Date		
		Day	Mth	Yr	Day	Mth	Yr
For SB							
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For SB							

*An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.*

*All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome If patient died, STOP: go to the COPD SAE section and follow instructions given there	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent ☐ Constant	☐ Intermittent ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____ Date : _____		



SmithKline Beecham
Pharmaceuticals

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*An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.*

*All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no further COPD exacerbations or changes to COPD exacerbations have occurred since the previous module please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to the COPD SAE section and follow instructions given there</i>	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy <i>If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate</i>	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____ Date : Day Month Yr		



SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number	Patient Initials		
207499/040		0 0 0 0			

*An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.*

*All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to the COPD SAE section and follow instructions given there</i>	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy <i>If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate</i>	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

Date :

Day	Month	Yr			

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)**SAEs MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS****COMPLETE THE SAE PAGES OPPOSITE**

Please complete these pages as fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Experience Course' blank and update it later

SIGN AND DATE THE SAE PAGE**PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE**

- Demography
- Significant Medical/Surgical History and Physical Examination
- Study Medication Record
- Concomitant Medication
- Form D (if applicable)

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE
(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO:

Your local SB CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local SB CRA/Medical monitor within 24 hours

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number _____ . ____
Serious Adverse Experience <i>(Please print clearly)</i>	COPD Exacerbation	→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	____ Day ____ Month ____ Yr ____ 24hr: ____ min	
End Date and Time <i>(If ongoing please leave blank)</i>	____ Day ____ Month ____ Yr ____ 24hr: ____ min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ____ ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) <i>Please specify</i> _____ ☐ Another condition (eg, condition under study, intercurrent illness) <i>Please specify</i> _____ ☐ Another drug <i>Please specify</i> _____
Corrective Therapy <i>If 'Yes', record details in the COPD Medication or Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 	SB Receipt Date			
				Day	Month	Year	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	 Day Month Yr			
	 Day Month Yr			
	 Day Month Yr			
	 Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes
Randomisation / Study Medication Number: **Investigator's Signature:**

(confirming that the above data are accurate and complete)

Date

Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

Day	Month	Year

Please PRINT Name

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Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date		
207499/040				Day	Month	Year
		0 0 0 0 0				

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

Person Reporting SAE _____ (Please print clearly)		AEGIS Number
Serious Adverse Experience (Please print clearly)	COPD Exacerbation	→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	
Outcome If patient died, please complete Form D	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) Please specify _____ ☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____ ☐ Another drug Please specify _____
Corrective Therapy If 'Yes', record details in the COPD Medication or Procedures section	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]	SB Receipt Date Day Month Year [][][][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

[]	[]	[]	[]	[]

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

[][]	[][]	[][]
Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

[][]	[][]	[][]
Day	Month	Year

Please PRINT Name

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Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]		

MEDICATION FOR COPD EXACERBATIONS

Has the patient taken any medication for COPD exacerbations since the previous module?							
☐ No ☐ Yes → <i>If 'Yes', please record details below</i>							
Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible) Day Mth Yr	End Date (or if Continuing mark box) Day Mth Yr	
				COPD EXACERBATION	[][][][][][]	[][][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][][]	[][][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][][]	[][][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][][]	[][][][][][]	☐
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				COPD EXACERBATION	[][][][][][]	[][][][][][]	☐
For SB							
* For Route, see tab for acceptable abbreviations.							

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Protocol	Centre Number	Patient Number	Patient Initials		
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MEDICAL PROCEDURES

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since the previous module?

☐ No

☐ Yes → If 'Yes', please record details below using standard medical terminology

Procedure	Indication	Procedure Start Date			Procedure End Date		
		Day	Mth	Yr	Day	Mth	Yr
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
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	COPD EXACERBATION						
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Protocol 207499/040	Centre Number <table border="1"><tr><td></td><td></td><td></td></tr></table>				Patient Number <table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						
0	0	0	0	0													

HEALTHCARE RESOURCE UTILISATION FOR COPD EXACERBATIONS

Complete this form for any COPD exacerbation related medical care the patient received since the previous module

Physician Visits (i.e., COPD care excluding scheduled protocol visits)

☐ There were no physician visits since the previous module

Date of Visit Day Mth Yr	Reason for Visit						
<table border="1"><tr><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>							
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Emergency Room (ER)/Urgent Care Visits/Casualty Department Procedures (i.e., lung surgery)

☐ There were no Emergency Room/Urgent Care Visits/Casualty Department Procedures since previous module

Date of Visit Day Mth Yr	Reason for Visit	Patient Admitted from ER?							
		Yes	No						
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Protocol 207499/040	Centre Number <table border="1"><tr><td></td><td></td><td></td></tr></table>				Patient Number <table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						
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HEALTHCARE RESOURCE UTILISATION FOR COPD EXACERBATIONS - (cont)

Hospitalisations (also record details of any hospitalisation in the Serious Adverse Experience - COPD Exacerbation section)

☐ There were no hospitalisations since the previous module

Date of Admission Day Mth Yr	Date of Discharge Day Mth Yr	Reason for Admission										
<table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>						<table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>						
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Intensive Care Unit (ICU) stays (did the patient stay in the ICU during any of the above hospitalisations?)

☐ There were no ICU stays since previous module

Date Admitted to ICU Day Mth Yr	Date Discharged from ICU Day Mth Yr	Reason for ICU Admission										
<table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>						<table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>						
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Lost Work Days (i.e., days patient missed work due to COPD excluding scheduled protocol visits)

☐ There were no lost work days since the previous module

Stop Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence										
<table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>						<table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>						
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Protocol	Centre Number	Patient Number	Patient Initials		
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STUDY CONTINUATION/WITHDRAWAL

Is the patient continuing in the study?

☐ Yes☐ No →

*If 'No' please mark the **primary** cause of withdrawal and enter the date of the final visit and the date of the final dose*

[1] ☐ Adverse experience (complete AE or SAE section)[2] ☐ Insufficient therapeutic effect[3] ☐ Protocol deviation (including non-compliance)[4] ☐ Lost to follow-up[7] ☐ Other - specify: _____

Date of Final Visit

Day	Month	Yr	

Date of Final dose

Day	Month	Yr	

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data on this case report form and that all information is complete and accurate.

Investigator's Signature

Date

Day	Month	Yr

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)

SAEs MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS

COMPLETE THE SAE PAGES OPPOSITE

Please complete these pages as fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Experience Course' blank and update it later

SIGN AND DATE THE SAE PAGE**PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE**

- Demography
- Significant Medical/Surgical History and Physical Examination
- Study Medication Record
- Medical Procedures
- Concomitant Medication
- Form D (if applicable)

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE

(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO:

Your local SB CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local SB CRA/Medical monitor within 24 hours

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Protocol	Centre Number	Patient Number	Patient Initials		
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MOD17 & MOD18 - SERIOUS ADVERSE EXPERIENCES

MOD17 & MOD18	Serious Adverse Experiences
MOD17 :	281, 282
MOD18	283, 284

Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date		
				Day	Month	Year
207499/040		0 0 0 0 0				

Patient Reporting SAE <i>(Please print clearly)</i>		AEGIS Number _____ . ____
Serious Adverse Experience <i>(Please print clearly)</i>		→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	____ Day ____ Month ____ Yr ____ 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	____ Day ____ Month ____ Yr ____ 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ____ ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) <i>Please specify</i> _____ ☐ Another condition (eg, condition under study, intercurrent illness) <i>Please specify</i> _____ ☐ Another drug <i>Please specify</i> _____
Corrective Therapy <i>If 'Yes', record details in the Concomitant Medication or Medical Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]	SB Receipt Date Day Month Year [][][][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

[]	[]	[]	[]	[]

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

[][]	[][]	[][]
Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

[][]	[][]	[][]
Day	Month	Year

Please PRINT Name

Person Reporting SAE (Please print clearly)		AEGIS Number
Serious Adverse Experience (Please print clearly)		→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	
End Date and Time (If ongoing please leave blank)	Day Month Yr 24hr:min	
Outcome If patient died, please complete Form D	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) Please specify _____ ☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____ ☐ Another drug Please specify _____
Corrective Therapy If 'Yes', record details in the Concomitant Medication or Medical Procedures section	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]	SB Receipt Date Day Month Year [][][][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

[][][][][]

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

[][]	[][][]	[][]
Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

[][]	[][][]	[][]
Day	Month	Year

Please PRINT Name

Protocol	Centre Number	Patient Number	Patient Initials
207499/040		0 0 0 0 0	

CONFIDENTIAL*PROTOCOL 207499/040**BOOK 7 : VISITS 15 AND 16 (WEEKS 48 AND 52)*

***A MULTICENTRE, OPEN-LABEL EXTENSION STUDY TO EVALUATE
THE SAFETY, TOLERABILITY AND EFFICACY OF ORAL SB 207499
(15mg TWICE DAILY) IN PATIENTS WITH CHRONIC OBSTRUCTIVE
PULMONARY DISEASE (COPD)***

GENERAL INSTRUCTIONS

- Write clearly in capital letters using a black ball point pen and press firmly so that all copies are legible
- Do not write in shaded areas
- Answer ALL questions on every page
- Enter "N/A" if information requested is not available
- Initial and date all changes, additions or deletions. Use a single pen stroke to remove an incorrect entry
- Enter the patient initials on all pages on which information has been entered and the patient number and centre number where required

Do not enter additional data/information after the set of CRF pages has been split/separated

The cover flap or plastic writing board should be used to divide each set of pages before writing on them with a ball point pen

DATE

Please use the following three-letter abbreviations for the months

January	JAN
February	FEB
March	MAR
April	APR
May	MAY
June	JUN
July	JUL
August	AUG
September	SEP
October	OCT
November	NOV
December	DEC

e.g.

0	1	J	A	N	9	9
Day		Month			Year	

 = 1st January 1999

TIME

Unless specified otherwise, please use the 24 hour clock

e.g.

1	5	3	0
24hr:min			

 = 3.30 p.m

PATIENT INITIALS

Please use the following format:

e.g.

ROUTE KEY FOR PRIOR/CONCOMITANT MEDICATION PAGE

PO = By mouth	SL = Sublingual	TD = Transdermal
IV = Intravenous	IT = Intrathecal	IH = Inhaled
IM = Intramuscular	VA = Vaginal	SC = Subcutaneous
IAR = Intra-arterial	NA = Nasal	PR = Rectal
TO = Topical	IA = Intra-articular injection	ID = Intradermal

**SUMMARY CHART OF STUDY PROCEDURES (OPEN BOXES)
PROTOCOL SB 207499/040***Mark open boxes to confirm that each procedure has been completed.*

Procedures	Visit 15	Visit 16
	Week 48	Week 52
Signed written informed consent		
Study Medication compliance		
Concomitant Medication		
Diary Card Review ⁷		
Adverse Experiences ⁸		
COPD Exacerbation assessment/Healthcare Ut.		
Physical (Including Respiratory) Examination		
Resting 12-Lead ECG		
Vital Signs (BP, HR) ³		
Overall Breathlessness (Modified Borg)		
Exercise Tolerance Test - 6 Minute Walk		
Post Exercise Breathlessness		
Pulmonary Function Tests ⁴		
Laboratory Tests ⁵		
Pregnancy Test ⁶		
Quality of Life Assessment: SGRQ		
Quality of Life Assessment: SF-36		
Dispense or re-dispense Open-Label Medication		
Study Continuation / Withdrawal		

³ *Orthostatic blood pressure and heart rate are measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal.*

⁴ *To include FEV₁, FEV₆, FVC, FEF₂₅₋₇₅, FEF₇₅, and PEFR.*

⁵ *Faecal occult blood is measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal. Baseline measure is taken from last FOB in Study 042 or Study 091*

⁶ *Serum pregnancy test for female patients of child bearing potential. Urine test only is done at Follow-Up Visit.*

⁷ *A Diary Card is issued at each visit. The patient will use the Diary Card to record if they feel different since the previous visit.*

⁸ *Patients will be assessed for GI AEs at every visit.*

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Protocol	Centre Number	Patient Number	Patient Initials		
207499/040		0 0 0 0 0			

MODULE 19

Please do not split modules

Module 19 : Visit 15 (Week 48) and Visit 16 (Week 52), Adverse Experiences, Conmeds, Medical Procedures, COPD Exacerbations, Resource Utilisation, Continuation/ Withdrawal

CRF Pages 285 - 326

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

Visit 15 :
SGRQ
SF36

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Protocol	Centre Number	Patient Number	Patient Initials	Visit Date	Visit 15 Week 48
207499/040		0 0 0 0 0		Day Month Year	

PRESENTATION TO CLINIC

Record time of presentation to clinic

 24hr:min

Note: *Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.*

Record the date and time of the patient's last dose of short-acting beta₂ agonist

Day	Month	Yr	24hr:min		

Record the date and time of the patient's last dose of long-acting beta₂ agonist

Day	Month	Yr	24hr:min		

Record the date and time of the patient's last dose of anticholinergic

Day	Month	Yr	24hr:min		

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes → If 'Yes' please record time

 24hr:min
ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 15 Week 48

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of exacerbation (maximum intensity)	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][][]		Visit 15 Week 48

RESOURCE UTILISATION FOR COPD EXACERBATIONS

If the patient has received any COPD exacerbation related medical care since the previous visit, please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

*Review the diary card for illegible/incomplete entries **in the presence of the patient***

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD Exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes →

If 'Yes' record details in the Adverse Experience section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 15 Week 48

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	

Date and time of last dose of study medication prior to the study visit

[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70	[][]	[][]	[][]	[][]	[][][]

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance $\geq 80\%$ and $\leq 120\%$?

☐ No →

If 'No' please check the % compliance at the previous visit. If compliance was not $\geq 80\%$ and $\leq 120\%$ at the last visit, please withdraw the patient. Please complete the assessments for Visit 15 and the assessments for patients withdrawing or stopping the study at Visit 15, contained at the end of this visit.

☐ Yes

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 15 Week 48

SMOKING STATUS

Does the patient currently smoke?

☐ No☐ Yes → If 'Yes' please record the average number of cigarettes per day : [][]**PULMONARY REHABILITATION PROGRAMME**

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit?

☐ No☐ Yes**LABORATORY TESTS**

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential). Please refer to the instructions on the SBCL shipping form and manual.

Blood Sample Date

[][]	[][]	[][]
Day	Month	Yr

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below

Attach label here

Are there any **clinically significant worsenings** since the previous visit?☐ No☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module

Place the SBCL laboratory report in the plastic wallet at the back of this module

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials 		Visit 15 Week 48

URINALYSIS

Please perform urinalysis using the dipstick provided by SBCL and record the results in the patient notes.

Urine Sample Date

Day	Month	Yr		

Are the dipstick results negative?

☐ No →

If 'No' please send the sample to SBCL for microscopy

☐ Yes
Are there any **clinically significant worsenings** since the previous visit on the SBCL report?
☐ No

☐ Yes →

If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

PREGNANCY TEST

Is the patient a female of child-bearing potential?

☐ No

☐ Yes →

If 'Yes' please request a pregnancy test on the SBCL requisition form.

Is the patient pregnant?

☐ No

☐ Yes →

If 'Yes' please withdraw the patient from the study, enter details in the Adverse Experience section. Complete the Early Withdrawal Visit (found in a separate book).

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Protocol		Patient Number	Patient Initials		Visit 15 Week 48
207499/040		0 0 0 0 0			

OVERALL BREATHLESSNESS ASSESSMENT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 15 Week 48

INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed: [][] / [][] / [][]
Day Month Yr

Were any clinically significant changes noted since the last visit?

☐ No

☐ Yes → ☐ Improvement

☐ Worsening →

Enter details in the Adverse Experience section at the back of this module.

Place the ECG trace in the plastic wallet at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 15 Week 48

VITAL SIGNS - ORTHOSTATIC CHANGE**1st Measurement: After 5 Minutes Supine**

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the previous assessment?☐ No☐ Yes → If 'Yes' record details in the Adverse Experience section at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 15 Week 48
207499/040		0 0 0 0 0			

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes. If the patient was too ill to attempt the test, please mark the 'Yes' box and enter 0 for distance walked.

☐ No

☐ Yes → If 'Yes', Distance walked Metres

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

POST-EXERCISE BREATHLESSNESS (Immediately after the patient completes the exercise tolerance)
Heart Rate beats/min
Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

- 0 Nothing at all
- 1 Very, very slight (just noticeable)
- 2 Very slight
- 3 Moderate
- 4 Somewhat severe
- 5 Severe
- 6
- 7 Very severe
- 8
- 9 Very, very severe (almost maximal)
- 10 Maximal

Post-exercise breathlessness score

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise tolerance test (rest for at least 10 minutes) before performing the pulmonary function tests.

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PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and/or anticholinergic medications and/or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

STUDY MEDICATION LABEL

Issue the patient one bottle of open-label study medication (70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

**Attach study medication
label here**

Give the patient the first dose of study medication with food and record the date and time of administration below.

Date and time of administration

Day	Month	Yr	24hr:	min			

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INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐ No →

If 'No' please complete the assessments for Visit 15 and issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-Up Visit. Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return in 7 +/- 3 days for a Follow-Up Visit.

☐ Yes →

If 'Yes' please:

- *Issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the next visit.*
- *Issue a new diary card. Remind the patient to record if they feel differently since starting the study*
- *Ask the patient to return for the next visit in 28 + / - 6 days.*
- **Remind the patient:**
 - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*
 - ii **not** *to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*
 - iii *to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for 2 hours and beta-2 agonists (long-acting) for 12 hours before the next visit.*
 - iv *to refrain from smoking for 2 hours immediately preceding the visit.*
 - v *to bring back at the next visit any remaining study medication or study medication containers and the diary card.*
 - vi *to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.*

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				Day	Month	Year	
		0 0 0 0 0					

PRESENTATION TO CLINIC

Record time of presentation to clinic

24hr:min

Note: Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.

Record the date and time of the patient's last dose of short-acting beta₂ agonist

Day Month Yr 24hr:min
Record the date and time of the patient's last dose of long-acting beta₂ agonist

Day Month Yr 24hr:min

Record the date and time of the patient's last dose of anticholinergic

Day Month Yr 24hr:min

Has the patient smoked within the past 2 hours?

☐ No☐ Yes → If 'Yes' please record time

24hr:min
COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	 Day Month Yr	 Day Month Yr	 Day Month Yr	 Day Month Yr
Level of exacerbation (maximum intensity)	☐ Level 1	☐ Level 1	☐ Level 1	☐ Level 1
	☐ Level 2	☐ Level 2	☐ Level 2	☐ Level 2
	☐ Level 3	☐ Level 3	☐ Level 3	☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.

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RESOURCE UTILISATION FOR COPD EXACERBATIONS

Please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

Review the diary card for illegible/incomplete entries **in the presence of the patient**

ADVERSE EXPERIENCES

Please complete the Adverse Experience section at the back of this module. If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

Please complete the Concomitant Medication section at the back of this module. If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD Exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.

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FAECAL OCCULT BLOOD TEST

Record the results of the faecal occult blood tests performed between visits 15 and 16

Test	Date of Collection Day Mth Yr	Was the faecal occult blood test positive ?
1	[][][][][][]	☐ No ☐ Yes
2	[][][][][][]	☐ No ☐ Yes
3	[][][][][][]	☐ No ☐ Yes

Are these findings clinically significant ?

☐ No

☐ Yes → If 'Yes' record details in the Adverse Experiences section at the back of this module.

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STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)
[][][][][][]	[][][][][][]	[]	
[][][][][][]	[][][][][][]	[]	
[][][][][][]	[][][][][][]	[]	

Date and time of last dose of study medication prior to the study visit

[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70	[][]	[][]	[][]	[][]	[][][][]

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance $\geq 80\%$ and $\leq 120\%$?

☐ No →

If 'No' please check the % compliance at the previous visit. If compliance was not $\geq 80\%$ and $\leq 120\%$ at the last visit, please withdraw the patient. Please complete the assessments for Visit 16 and the assessments for patients withdrawing or stopping the study at Visit 16, contained at the end of this visit.

☐ Yes

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SMOKING STATUS

Does the patient currently smoke?

☐ No☐ Yes → If 'Yes' please record the average number of cigarettes per day : [][]**PULMONARY REHABILITATION PROGRAMME**

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit?

☐ No☐ Yes**LABORATORY TESTS**

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential). Please refer to the instructions on the SBCL shipping form and manual.

Blood Sample Date

[][]	[][]	[][]
Day	Month	Yr

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below

Attach label here

Are there any **clinically significant worsenings** since the previous visit?☐ No☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module

Place the SBCL laboratory report in the plastic wallet at the back of this module

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URINALYSIS

Please perform urinalysis using the dipstick provided by SBCL and record the results in the patient notes.

Urine Sample Date

Day	Month	Yr		

Are the dipstick results negative?

- ☐ No → If 'No' please send the sample to SBCL for microscopy
- ☐ Yes

Are there any **clinically significant worsenings** since the previous visit on the SBCL report?

- ☐ No
- ☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

PREGNANCY TEST

Is the patient a female of child-bearing potential?

- ☐ No
- ☐ Yes → If 'Yes' please request a pregnancy test on the SBCL requisition form.

Is the patient pregnant?

- ☐ No
- ☐ Yes → If 'Yes' please withdraw the patient from the study, enter details in the Adverse Experience section. Complete the Early Withdrawal Visit (found in a separate book).

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OVERALL BREATHLESSNESS ASSESSMENT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed: [][] / [][] / [][]
Day Month Yr

Were any clinically significant changes noted since the last visit?

☐ No

☐ Yes → ☐ Improvement

☐ Worsening →

Enter details in the Adverse Experience section at the back of this module.

Place the ECG trace in the plastic wallet at the back of this module.

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PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and/or anticholinergic medications and/or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

STUDY MEDICATION LABEL

Issue the patient one bottle of open-label study medication (70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

**Attach study medication
label here**

Give the patient the first dose of study medication with food and record the date and time of administration below.

Date and time of administration

Day	Month	Yr	24hr:	min			

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INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐ No →

If 'No' please complete the assessments for Visit 16 and the Assessments for Patients Withdrawing or Stopping the Study at Visit 16 contained on the following pages. Complete and fax the Withdrawal Form contained in the Withdrawal and Follow-Up Book.

☐ Yes →

If 'Yes' please:

- *Issue a new diary card. Remind the patient to record if they feel differently since starting the study*
- *Ask the patient to return for the next visit in 28 +/- 6 days.*
- *Complete the Study Continuation / Withdrawal page at the back of this module.*
- **Remind the patient:**
 - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*
 - ii **not** *to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*
 - iii *to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonists (long-acting) for **12 hours** before the next visit.*
 - iv *to refrain from smoking for **2 hours** immediately preceding the visit.*
 - v *to bring back at the next visit any remaining study medication or study medication containers and the diary card.*
 - vi *to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.*

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ASSESSMENTS FOR PATIENTS WITHDRAWING OR STOPPING THE STUDY

Complete the assessments below only for patients who are withdrawing early from the study or stopping the study because the product has been registered or because the sponsor has terminated the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a clinically significant worsening in the patient's physical condition since the previous examination?

☐ No

☐ Yes →

If 'Yes' record details in the Adverse Experience section at the back of this module.

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FAECAL OCCULT BLOOD TEST

Issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-Up Visit.

VITAL SIGNS - ORTHOSTATIC CHANGE**1st Measurement: After 5 Minutes Supine**

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

Are there any clinically significant worsenings since the previous assessment?

☐ No

☐ Yes → If 'Yes' record details in the Adverse Experience section at the back of this module.

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Follow-Up Visit in 7 +/- 3 days.

ADVERSE EXPERIENCES (Non-serious)**DEFINITIONS****INTENSITY (Maximum)**

MILD	<i>Adverse experience which is easily tolerated</i>
MODERATE	<i>Adverse experience sufficiently discomforting to interfere with daily activities</i>
SEVERE	<i>Adverse experience which prevents normal everyday activities</i>

RELATIONSHIP TO INVESTIGATIONAL DRUG

NOT RELATED	<i>The adverse experience is definitely not related to the test drug</i>
UNLIKELY	<i>There are other more likely causes and the drug is not suspected as a cause</i>
SUSPECTED (REASONABLE POSSIBILITY)	<i>A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug</i>
PROBABLE	<i>There probably is a direct cause and effect relationship between the adverse experience and the study drug</i>

SERIOUS ADVERSE EXPERIENCE (SAE)

An SAE is any event which is :-

- 1 - fatal
- 2 - life threatening
- 3 - disabling/incapacitating
- 4 - results in hospitalisation (excluding elective surgery or routine clinical procedures)
- 5 - prolongs a hospital stay
- 6 - associated with congenital abnormality
- 7 - cancer
- 8 - associated with overdose
- 9 - In addition any event which the investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug should be reported as a serious event

IF AN SAE OCCURS, PLEASE GO TO SAE SECTION IMMEDIATELY AND FOLLOW THE INSTRUCTIONS GIVEN THERE

Use each form for a maximum of two experiences

PLEASE REMEMBER ALL QUESTIONS ON ADVERSE EXPERIENCES FORM SHOULD BE COMPLETED

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ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous module?" Provide the diagnosis, **not** symptoms, where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbations section

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no adverse experiences occurred since the previous module, please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous module?" Provide the diagnosis, **not** symptoms, where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbations section

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no further adverse experiences or changes in adverse experiences occurred since the previous module, please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous module?" Provide the diagnosis, **not** symptoms, where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbations section

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no further adverse experiences or changes in adverse experiences occurred since the previous module, please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the previous module.
(Please write using BLOCK CAPITALS).

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

☐ No concomitant medication changes since the previous module

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experience section using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the new start and end date.

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)			
					Day	Mth	Yr	Day	Mth	Yr	
											☐
For SB											
											☐
For SB											
											☐
For SB											
											☐
For SB											
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											☐
For SB											
											☐
For SB											
* For Route, see tab for acceptable abbreviations.											

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CONCOMITANT MEDICATION - Continued

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experience section using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the new start and end date.

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)			
					Day	Mth	Yr	Day	Mth	Yr	
											☐
For SB											
											☐
For SB											
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For SB											
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											☐
For SB											

* For Route, see tab for acceptable abbreviations.

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MEDICAL PROCEDURES - (Excluding treatment for COPD Exacerbations)

Do not record procedures used to treat COPD exacerbations here, record them in the COPD Exacerbations section.

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed since the previous module?

☐ No

☐ Yes → If 'Yes', please record details below using standard medical terminology (Please print clearly)

All indications for procedures should be recorded in the Adverse Experience section

Procedure	Indication	Procedure Start Date			Procedure End Date		
		Day	Mth	Yr	Day	Mth	Yr
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							
For SB							



Protocol	Centre Number	Patient Number	Patient Initials		
207499/040					

DETAILS OF COPD EXACERBATIONS

*An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy. All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since the previous module please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome If patient died, STOP: go to the COPD SAE section and follow instructions given there	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____ Date : Day Month Yr		

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.

All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages**

If no further COPD exacerbations or changes to COPD exacerbations have occurred since the previous module please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome If patient died, STOP: go to the COPD SAE section and follow instructions given there ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.

All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages**

If no further COPD exacerbations or changes to COPD exacerbations have occurred since the previous module please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome If patient died, STOP: go to the COPD SAE section and follow instructions given there ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)**SAEs MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS****COMPLETE THE SAE PAGES OPPOSITE**

Please complete these pages as fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Experience Course' blank and update it later

SIGN AND DATE THE SAE PAGE**PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE**

- Demography
- Significant Medical/Surgical History and Physical Examination
- Study Medication Record
- Concomitant Medication
- Form D (if applicable)

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE
(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO:

Your local SB CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local SB CRA/Medical monitor within 24 hours

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience <i>(Please print clearly)</i>	COPD Exacerbation	→ <i>Specify reason(s) for considering this a serious AE. Mark all that apply.</i> [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) <i>Please specify</i> _____ ☐ Another condition (eg, condition under study, intercurrent illness) <i>Please specify</i> _____ ☐ Another drug <i>Please specify</i> _____
Corrective Therapy <i>If 'Yes', record details in the COPD Medication or Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]	SB Receipt Date Day Month Year [][][][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

[]	[]	[]	[]	[]

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

[][]	[][]	[][]
Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

[][]	[][]	[][]
Day	Month	Year

Please PRINT Name



SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date		
				Day	Month	Year
207499/040		0 0 0 0 0				

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience <i>(Please print clearly)</i>	COPD Exacerbation	→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	Day Month Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (<i>maximum</i>)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) Please specify _____ ☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____ ☐ Another drug Please specify _____
Corrective Therapy <i>If 'Yes', record details in the COPD Medication or Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]	SB Receipt Date			
				Day [][]	Month [][]	Year [][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	[][][][][][] Day Month Yr			
	[][][][][][] Day Month Yr			
	[][][][][][] Day Month Yr			
	[][][][][][] Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number: [][][][][]

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

[][]	[][]	[][]
Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

[][]	[][]	[][]
Day	Month	Year

Please PRINT Name

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Protocol 207499/040	Centre Number <table border="1"><tr><td></td><td></td><td></td></tr></table>				Patient Number <table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						
0	0	0	0	0													

MEDICATION FOR COPD EXACERBATIONSHas the patient taken any medication for **COPD exacerbations** since the previous module?☐ No☐ Yes → If 'Yes', please record details below

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)			
					Day	Mth	Yr	Day	Mth	Yr	
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											
* For Route, see tab for acceptable abbreviations.											

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Protocol	Centre Number	Patient Number	Patient Initials		
207499/040		0 0 0 0 0			

MEDICAL PROCEDURES FOR COPD EXACERBATIONS

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since the previous module?

☐ No

☐ Yes → If 'Yes', please record details below using standard medical terminology

Procedure	Indication	Procedure Start Date			Procedure End Date		
		Day	Mth	Yr	Day	Mth	Yr
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							

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Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]		

HEALTHCARE RESOURCE UTILISATION FOR COPD EXACERBATIONS

Complete this form for any **COPD exacerbation related medical care** the patient received since the previous module

Physician Visits (i.e., COPD care excluding scheduled protocol visits)

☐ There were no physician visits since the previous module

Date of Visit Day Mth Yr	Reason for Visit
[][][][][][]	
[][][][][][]	
[][][][][][]	
[][][][][][]	
[][][][][][]	
[][][][][][]	
[][][][][][]	
[][][][][][]	
[][][][][][]	

Emergency Room (ER)/Urgent Care Visits/Casualty Department Procedures (i.e., lung surgery)

☐ There were no Emergency Room/Urgent Care Visits/Casualty Department Procedures since previous module

Date of Visit Day Mth Yr	Reason for Visit	Patient Admitted from ER?	
		Yes	No
[][][][][][]		☐	☐
[][][][][][]		☐	☐
[][][][][][]		☐	☐
[][][][][][]		☐	☐
[][][][][][]		☐	☐
[][][][][][]		☐	☐
[][][][][][]		☐	☐

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Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]		

HEALTHCARE RESOURCE UTILISATION FOR COPD EXACERBATIONS - (cont)

Hospitalisations (also record details of any hospitalisation in the Serious Adverse Experience - COPD Exacerbation section)

☐ There were no hospitalisations since the previous module

Date of Admission Day Mth Yr	Date of Discharge Day Mth Yr	Reason for Admission
[][][][][][]	[][][][][][]	
[][][][][][]	[][][][][][]	
[][][][][][]	[][][][][][]	
[][][][][][]	[][][][][][]	

Intensive Care Unit (ICU) stays (did the patient stay in the ICU during any of the above hospitalisations?)

☐ There were no ICU stays since previous module

Date Admitted to ICU Day Mth Yr	Date Discharged from ICU Day Mth Yr	Reason for ICU Admission
[][][][][][]	[][][][][][]	
[][][][][][]	[][][][][][]	
[][][][][][]	[][][][][][]	
[][][][][][]	[][][][][][]	

Lost Work Days (i.e., days patient missed work due to COPD excluding scheduled protocol visits)

☐ There were no lost work days since the previous module

Stop Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence
[][][][][][]	[][][][][][]	
[][][][][][]	[][][][][][]	
[][][][][][]	[][][][][][]	
[][][][][][]	[][][][][][]	
[][][][][][]	[][][][][][]	
[][][][][][]	[][][][][][]	

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

STUDY CONTINUATION/WITHDRAWAL

Is the patient continuing in the study?

☐ Yes☐ No →

*If 'No' please mark the **primary** cause of withdrawal and enter the date of the final visit and the date of the final dose*

[1] ☐ Adverse experience (complete AE or SAE section)[2] ☐ Insufficient therapeutic effect[3] ☐ Protocol deviation (including non-compliance)[4] ☐ Lost to follow-up[5] ☐ Other - specify: _____

Date of Final Visit

Day	Month	Yr

Date of Final dose

Day	Month	Yr

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data on this case report form and that all information is complete and accurate.

Investigator's Signature

Date

Day	Month	Yr

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)

SAEs MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS

COMPLETE THE SAE PAGES OPPOSITE

Please complete these pages as fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Experience Course' blank and update it later

SIGN AND DATE THE SAE PAGE**PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE**

- Demography
- Significant Medical/Surgical History and Physical Examination
- Study Medication Record
- Medical Procedures
- Concomitant Medication
- Form D (if applicable)

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE

(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO:

Your local SB CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local SB CRA/Medical monitor within 24 hours

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Protocol	Centre Number	Patient Number	Patient Initials		
207499/040		0 0 0 0 0			

MOD20 & MOD21 - SERIOUS ADVERSE EXPERIENCES

MOD20 & MOD21	Serious Adverse Experiences
MOD20 :	327, 328
MOD21	329, 330

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience <i>(Please print clearly)</i>		→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	Day Month Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (<i>maximum</i>)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) Please specify _____ ☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____ ☐ Another drug Please specify _____
Corrective Therapy <i>If 'Yes', record details in the Concomitant Medication or Medical Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]	SB Receipt Date Day Month Year [][][][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

[][][][][]

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

[][]	[][][]	[][]
Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

[][]	[][][]	[][]
Day	Month	Year

Please PRINT Name

Person Reporting SAE (Please print clearly) _____		AEGIS Number
Serious Adverse Experience (Please print clearly)		→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	
End Date and Time (If ongoing please leave blank)	Day Month Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent ☐ Constant	→ No. of episodes
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	
Corrective Therapy <i>If 'Yes', record details in the Concomitant Medication or Medical Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) Please specify _____ ☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____ ☐ Another drug Please specify _____

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Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]	SB Receipt Date Day Month Year [][][][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number: [][][][][]

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

[][]	[][][]	[][]
Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

[][]	[][][]	[][]
Day	Month	Year

Please PRINT Name

Protocol	Centre Number	Patient Number	Patient Initials
207499/040		0 0 0 0 0	

CONFIDENTIAL*PROTOCOL 207499/040**BOOK 8 : VISITS 17 AND 18 (WEEKS 56 AND 60)*

***A MULTICENTRE, OPEN-LABEL EXTENSION STUDY TO EVALUATE
THE SAFETY, TOLERABILITY AND EFFICACY OF ORAL SB 207499
(15mg TWICE DAILY) IN PATIENTS WITH CHRONIC OBSTRUCTIVE
PULMONARY DISEASE (COPD)***

GENERAL INSTRUCTIONS

- Write clearly in capital letters using a black ball point pen and press firmly so that all copies are legible
- Do not write in shaded areas
- Answer ALL questions on every page
- Enter "N/A" if information requested is not available
- Initial and date all changes, additions or deletions. Use a single pen stroke to remove an incorrect entry
- Enter the patient initials on all pages on which information has been entered and the patient number and centre number where required

Do not enter additional data/information after the set of CRF pages has been split/separated

The cover flap or plastic writing board should be used to divide each set of pages before writing on them with a ball point pen

DATE

Please use the following three-letter abbreviations for the months

January	JAN
February	FEB
March	MAR
April	APR
May	MAY
June	JUN
July	JUL
August	AUG
September	SEP
October	OCT
November	NOV
December	DEC

e.g.

0	1	J	A	N	9	9
Day		Month			Year	

 = 1st January 1999

TIME

Unless specified otherwise, please use the 24 hour clock

e.g.

1	5	3	0
24hr:min			

 = 3.30 p.m

PATIENT INITIALS

Please use the following format:

e.g.

ROUTE KEY FOR PRIOR/CONCOMITANT MEDICATION PAGE

PO = By mouth	SL = Sublingual	TD = Transdermal
IV = Intravenous	IT = Intrathecal	IH = Inhaled
IM = Intramuscular	VA = Vaginal	SC = Subcutaneous
IAR = Intra-arterial	NA = Nasal	PR = Rectal
TO = Topical	IA = Intra-articular injection	ID = Intradermal

SUMMARY CHART OF STUDY PROCEDURES (OPEN BOXES)
PROTOCOL SB 207499/040

Mark open boxes to confirm that each procedure has been completed.

Procedures	Visit 17 Week 56	Visit 18 Week 60
Signed written informed consent		
Study Medication compliance		
Concomitant Medication		
Diary Card Review ⁷		
Adverse Experiences ⁸		
COPD Exacerbation assessment/Healthcare Ut.		
Physical (Including Respiratory) Examination		
Resting 12-Lead ECG		
Vital Signs (BP, HR) ³		
Overall Breathlessness (Modified Borg)		
Exercise Tolerance Test - 6 Minute Walk		
Post Exercise Breathlessness		
Pulmonary Function Tests ⁴		
Laboratory Tests ⁵		
Pregnancy Test ⁶		
Quality of Life Assessment: SGRQ		
Quality of Life Assessment: SF-36		
Dispense or re-dispense Open-Label Medication		
Study Continuation / Withdrawal		

³ *Orthostatic blood pressure and heart rate are measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal.*

⁴ *To include FEV₁, FEV₆, FVC, FEF₂₅₋₇₅, FEF₇₅, and PEFR.*

⁵ *Faecal occult blood is measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal. Baseline measure is taken from last FOB in Study 042 or Study 091*

⁶ *Serum pregnancy test for female patients of child bearing potential. Urine test only is done at Follow-Up Visit.*

⁷ *A Diary Card is issued at each visit. The patient will use the Diary Card to record if they feel different since the previous visit.*

⁸ *Patients will be assessed for GI AEs at every visit.*

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Protocol	Centre Number	Patient Number	Patient Initials		
207499/040		0 0 0 0 0			

MODULE 22

Please do not split modules

Module 22 : Visit 17 (Week 56) and Visit 18 (Week 60), Adverse Experiences, Conmeds, Medical Procedures, COPD Exacerbations, Resource Utilisation, Continuation/Withdrawal

CRF Pages 331 - 372

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

None

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Protocol 207499/040	Centre Number	Patient Number	Patient Initials	Visit Date			Visit 17 Week 56
				Day	Month	Year	
		0 0 0 0 0					

PRESENTATION TO CLINIC

Record time of presentation to clinic

 24hr:min

Note: Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.

Record the date and time of the patient's last dose of short-acting beta₂ agonist

Day	Month	Yr			

 24hr:min
Record the date and time of the patient's last dose of long-acting beta₂ agonist

Day	Month	Yr			

 24hr:min

Record the date and time of the patient's last dose of anticholinergic

Day	Month	Yr			

 24hr:min

Has the patient smoked within the past 2 hours?

☐ No☐ Yes → If 'Yes' please record time

 24hr:min
COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	<table border="1"> <tr> <td></td> <td></td> <td></td> </tr> <tr> <td>Day</td> <td>Month</td> <td>Yr</td> </tr> </table>				Day	Month	Yr	<table border="1"> <tr> <td></td> <td></td> <td></td> </tr> <tr> <td>Day</td> <td>Month</td> <td>Yr</td> </tr> </table>				Day	Month	Yr	<table border="1"> <tr> <td></td> <td></td> <td></td> </tr> <tr> <td>Day</td> <td>Month</td> <td>Yr</td> </tr> </table>				Day	Month	Yr	<table border="1"> <tr> <td></td> <td></td> <td></td> </tr> <tr> <td>Day</td> <td>Month</td> <td>Yr</td> </tr> </table>				Day	Month	Yr
Day	Month	Yr																										
Day	Month	Yr																										
Day	Month	Yr																										
Day	Month	Yr																										
Level of exacerbation (maximum intensity)	☐ Level 1	☐ Level 1	☐ Level 1	☐ Level 1																								
	☐ Level 2	☐ Level 2	☐ Level 2	☐ Level 2																								
	☐ Level 3	☐ Level 3	☐ Level 3	☐ Level 3																								

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 17 Week 56

RESOURCE UTILISATION FOR COPD EXACERBATIONS

If the patient has received any COPD exacerbation related medical care since the previous visit, please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

*Review the diary card for illegible/incomplete entries **in the presence of the patient***

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD Exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 17 Week 56

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	

Date and time of last dose of study medication prior to the study visit

[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70	[][]	[][]	[][]	[][]	[][][]

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance $\geq 80\%$ and $\leq 120\%$?

☐ No →

If 'No' please check the % compliance at the previous visit. If compliance was not $\geq 80\%$ and $\leq 120\%$ at the last visit, please withdraw the patient. Please complete the assessments for Visit 17 and the assessments for patients withdrawing or stopping the study at Visit 17, contained at the end of this visit.

☐ Yes

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 17 Week 56

SMOKING STATUS

Does the patient currently smoke?

☐ No☐ Yes → If 'Yes' please record the average number of cigarettes per day : [][]**PULMONARY REHABILITATION PROGRAMME**

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit?

☐ No☐ Yes**LABORATORY TESTS**

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential). Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date

[][]	[][]	[][]
Day	Month	Yr

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below

Attach label here

Are there any **clinically significant worsenings** since the previous visit?☐ No☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module

Place the Quest laboratory report in the plastic wallet at the back of this module

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][][]		Visit 17 Week 56

URINALYSIS

Please perform urinalysis using the dipstick provided by Quest and record the results in the patient notes.

Urine Sample Date

[][]	[][]	[][]
Day	Month	Yr

Are the dipstick results negative?

☐

No →

If 'No' please send the sample to Quest for microscopy☐

Yes

Are there any **clinically significant worsenings** since the previous visit on the Quest report?☐

No

☐

Yes →

*If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.***PREGNANCY TEST**

Is the patient a female of child-bearing potential?

☐

No

☐

Yes →

If 'Yes' please request a pregnancy test on the Quest requisition form.

Is the patient pregnant?

☐

No

☐

Yes →

If 'Yes' please withdraw the patient from the study, enter details in the Adverse Experience section. Complete the Early Withdrawal Visit (found in a separate book).

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207499/040		0 0 0 0 0			

OVERALL BREATHLESSNESS ASSESSMENT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 17 Week 56

INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed: [][] / [][] / [][]
Day Month Yr

Were any clinically significant changes noted since the last visit?

☐ No

☐ Yes → ☐ Improvement

☐ Worsening →

Enter details in the Adverse Experience section at the back of this module.

Place the ECG trace in the plastic wallet at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 17 Week 56
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PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and/or anticholinergic medications and/or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

STUDY MEDICATION LABEL

Issue the patient one bottle of open-label study medication (70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

Attach study medication
label here

Give the patient the first dose of study medication with food and record the date and time of administration below.

Date and time of administration

Day	Month	Yr	24hr	:	min		

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Protocol		Patient Number	Patient Initials		Visit 17 Week 56
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INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐ No →

If 'No' please complete the assessments for Visit 17 and the Assessments for Patients Withdrawing or Stopping the Study at Visit 17 contained on the following pages. Complete and fax the Withdrawal Form contained in the Withdrawal and Follow-Up Book.

☐ Yes →

If 'Yes' please:

- *Issue a new diary card. Remind the patient to record if they feel differently since starting the study*
- *Ask the patient to return for the next visit in 28 + / - 6 days.*
- **Remind the patient:**
 - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*
 - ii **not** *to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*
 - iii *to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonists (long-acting) for **12 hours** before the next visit.*
 - iv *to refrain from smoking for **2 hours** immediately preceding the visit.*
 - v *to bring back at the next visit any remaining study medication or study medication containers and the diary card.*
 - vi *to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.*

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Protocol		Patient Number	Patient Initials		Visit 17 Week 56
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ASSESSMENTS FOR PATIENTS WITHDRAWING OR STOPPING THE STUDY

Complete the assessments below only for patients who are withdrawing early from the study or stopping the study because the product has been registered or because the sponsor has terminated the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes →

If 'Yes' record details in the Adverse Experience section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 17 Week 56

FAECAL OCCULT BLOOD TEST

Issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-Up Visit.

VITAL SIGNS - ORTHOSTATIC CHANGE**1st Measurement: After 5 Minutes Supine**

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

Are there any clinically significant worsenings since the previous assessment?

☐ No

☐ Yes →

If 'Yes' record details in the Adverse Experience section at the back of this module.

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Follow-Up Visit in 7 +/- 3 days.

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Protocol	Centre Number	Patient Number	Patient Initials	Visit Date	Visit 18 Week 60
207499/040		0 0 0 0 0		Day Month Year	

PRESENTATION TO CLINIC

Record time of presentation to clinic

24hr:min	

Note: *Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.*

Record the date and time of the patient's last dose of short-acting beta₂ agonist

Day	Month	Yr	24hr:min

Record the date and time of the patient's last dose of long-acting beta₂ agonist

Day	Month	Yr	24hr:min

Record the date and time of the patient's last dose of anticholinergic

Day	Month	Yr	24hr:min

Has the patient smoked within the past 2 hours?

☐ No☐ Yes → If 'Yes' please record time

24hr:min	

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 18 Week 60

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of exacerbation (maximum intensity)	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.

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Protocol		Patient Number	Patient Initials		Visit 18 Week 60
207499/040		0 0 0 0 0			

RESOURCE UTILISATION FOR COPD EXACERBATIONS

Please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

Review the diary card for illegible/incomplete entries **in the presence of the patient**

ADVERSE EXPERIENCES

Please complete the Adverse Experience section at the back of this module. If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

Please complete the Concomitant Medication section at the back of this module. If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD Exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 18 Week 60

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)
[][][][][][]	[][][][][][]	[]	
[][][][][][]	[][][][][][]	[]	
[][][][][][]	[][][][][][]	[]	

Date and time of last dose of study medication prior to the study visit

[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70	[][]	[][]	[][]	[][]	[][][][]

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance $\geq 80\%$ and $\leq 120\%$?

☐ No →

If 'No' please check the % compliance at the previous visit. If compliance was not $\geq 80\%$ and $\leq 120\%$ at the last visit, please withdraw the patient. Please complete the assessments for Visit 18 and the assessments for patients withdrawing or stopping the study at Visit 18, contained at the end of this visit.

☐ Yes

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 18 Week 60

SMOKING STATUS

Does the patient currently smoke?

☐ No☐ Yes → If 'Yes' please record the average number of cigarettes per day : [][]**PULMONARY REHABILITATION PROGRAMME**

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit?

☐ No☐ Yes**LABORATORY TESTS**

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential). Please refer to the instructions on the SBCL shipping form and manual.

Blood Sample Date

[][]	[][]	[][]
Day	Month	Yr

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below

Attach label here

Are there any **clinically significant worsenings** since the previous visit?☐ No☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module

Place the SBCL laboratory report in the plastic wallet at the back of this module

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][][]		Visit 18 Week 60

URINALYSIS

Please perform urinalysis using the dipstick provided by SBCL and record the results in the patient notes.

Urine Sample Date

Day	Month	Yr		

Are the dipstick results negative?

- ☐ No → If 'No' please send the sample to SBCL for microscopy
- ☐ Yes

Are there any **clinically significant worsenings** since the previous visit on the SBCL report?

- ☐ No
- ☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

PREGNANCY TEST

Is the patient a female of child-bearing potential?

- ☐ No
- ☐ Yes → If 'Yes' please request a pregnancy test on the SBCL requisition form.

Is the patient pregnant?

- ☐ No
- ☐ Yes → If 'Yes' please withdraw the patient from the study, enter details in the Adverse Experience section. Complete the Early Withdrawal Visit (found in a separate book).

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Protocol		Patient Number	Patient Initials		Visit 18 Week 60
207499/040		0 0 0 0 0			

OVERALL BREATHLESSNESS ASSESSMENT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 18 Week 60

INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed: [][] / [][] / [][]
Day Month Yr

Were any clinically significant changes noted since the last visit?

☐ No

☐ Yes →

☐ Improvement

☐ Worsening →

Enter details in the Adverse Experience section at the back of this module.

Place the ECG trace in the plastic wallet at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 18 Week 60
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EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes. If the patient was too ill to attempt the test, please mark the 'Yes' box and enter 0 for distance walked.

☐ No

☐ Yes → If 'Yes', Distance walked Metres

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

POST-EXERCISE BREATHLESSNESS (Immediately after the patient completes the exercise tolerance)
Heart Rate beats/min
Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

- 0 Nothing at all
- 1 Very, very slight (just noticeable)
- 2 Very slight
- 3 Moderate
- 4 Somewhat severe
- 5 Severe
- 6
- 7 Very severe
- 8
- 9 Very, very severe (almost maximal)
- 10 Maximal

Post-exercise breathlessness score

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise tolerance test (rest for at least 10 minutes) before performing the pulmonary function tests.

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Protocol		Patient Number	Patient Initials		Visit 18 Week 60
207499/040		0 0 0 0 0			

PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and/or anticholinergic medications and/or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

STUDY MEDICATION LABEL

Issue the patient one bottle of open-label study medication (70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

Attach study medication
label here

Give the patient the first dose of study medication with food and record the date and time of administration below.

Date and time of administration

Day	Month	Yr	24hr	:	min		

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][][]		Visit 18 Week 60

INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐ No →

If 'No' please complete the assessments for Visit 18 and the Assessments for Patients Withdrawing or Stopping the Study at Visit 18 contained on the following pages. Complete and fax the Withdrawal Form contained in the Withdrawal and Follow-Up Book.

☐ Yes →

If 'Yes' please:

- *Issue a new diary card. Remind the patient to record if they feel differently since starting the study*
- *Ask the patient to return for the next visit in 28 +/- 6 days.*
- *Complete the Study Continuation / Withdrawal page at the back of this module.*
- **Remind the patient:**
 - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*
 - ii **not** *to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*
 - iii *to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonists (long-acting) for **12 hours** before the next visit.*
 - iv *to refrain from smoking for **2 hours** immediately preceding the visit.*
 - v *to bring back at the next visit any remaining study medication or study medication containers and the diary card.*
 - vi *to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.*

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 18 Week 60

ASSESSMENTS FOR PATIENTS WITHDRAWING OR STOPPING THE STUDY

Complete the assessments below only for patients who are withdrawing early from the study or stopping the study because the product has been registered or because the sponsor has terminated the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a clinically significant worsening in the patient's physical condition since the previous examination?

☐ No

☐ Yes →

If 'Yes' record details in the Adverse Experience section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 18 Week 60

FAECAL OCCULT BLOOD TEST

Issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-Up Visit.

VITAL SIGNS - ORTHOSTATIC CHANGE**1st Measurement: After 5 Minutes Supine**

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

Are there any clinically significant worsenings since the previous assessment?

☐ No

☐ Yes → If 'Yes' record details in the Adverse Experience section at the back of this module.

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Follow-Up Visit in 7 +/- 3 days.

ADVERSE EXPERIENCES (Non-serious)**DEFINITIONS****INTENSITY (Maximum)**

MILD	<i>Adverse experience which is easily tolerated</i>
MODERATE	<i>Adverse experience sufficiently discomforting to interfere with daily activities</i>
SEVERE	<i>Adverse experience which prevents normal everyday activities</i>

RELATIONSHIP TO INVESTIGATIONAL DRUG

NOT RELATED	<i>The adverse experience is definitely not related to the test drug</i>
UNLIKELY	<i>There are other more likely causes and the drug is not suspected as a cause</i>
SUSPECTED (REASONABLE POSSIBILITY)	<i>A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug</i>
PROBABLE	<i>There probably is a direct cause and effect relationship between the adverse experience and the study drug</i>

SERIOUS ADVERSE EXPERIENCE (SAE)

An SAE is any event which is :-

- 1 - fatal
- 2 - life threatening
- 3 - disabling/incapacitating
- 4 - results in hospitalisation (excluding elective surgery or routine clinical procedures)
- 5 - prolongs a hospital stay
- 6 - associated with congenital abnormality
- 7 - cancer
- 8 - associated with overdose
- 9 - In addition any event which the investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug should be reported as a serious event

IF AN SAE OCCURS, PLEASE GO TO SAE SECTION IMMEDIATELY AND FOLLOW THE INSTRUCTIONS GIVEN THERE

Use each form for a maximum of two experiences

PLEASE REMEMBER ALL QUESTIONS ON ADVERSE EXPERIENCES FORM SHOULD BE COMPLETED

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous module?" Provide the diagnosis, **not** symptoms, where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbations section

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no adverse experiences occurred since the previous module, please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

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Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
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Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
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Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

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Do not record COPD exacerbations here, record them in the COPD Exacerbations section

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Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
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Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the previous module.
(Please write using BLOCK CAPITALS).

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

☐ No concomitant medication changes since the previous module

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experience section using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the new start and end date.

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)																																	
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* For Route, see tab for acceptable abbreviations.																																									

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CONCOMITANT MEDICATION - Continued

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experience section using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the new start and end date.

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)			
					Day	Mth	Yr	Day	Mth	Yr	
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* For Route, see tab for acceptable abbreviations.

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MEDICAL PROCEDURES - (Excluding treatment for COPD Exacerbations)

Do not record procedures used to treat COPD exacerbations here, record them in the COPD Exacerbations section.

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed since the previous module?

☐ No

☐ Yes → If 'Yes', please record details below using standard medical terminology (Please print clearly)

All indications for procedures should be recorded in the Adverse Experience section

Procedure	Indication	Procedure Start Date			Procedure End Date		
		Day	Mth	Yr	Day	Mth	Yr
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*An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy. All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome If patient died, STOP: go to the COPD SAE section and follow instructions given there	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____ Date : Day Month Yr		

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DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.

All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages**

If no further COPD exacerbations or changes to COPD exacerbations have occurred since the previous module please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
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Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

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If no further COPD exacerbations or changes to COPD exacerbations have occurred since the previous module please sign the form below and mark this box. ☐

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Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)**SAEs MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS****COMPLETE THE SAE PAGES OPPOSITE**

Please complete these pages as fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Experience Course' blank and update it later

SIGN AND DATE THE SAE PAGE**PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE**

- Demography
- Significant Medical/Surgical History and Physical Examination
- Study Medication Record
- Concomitant Medication
- Form D (if applicable)

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE
(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO:

Your local SB CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local SB CRA/Medical monitor within 24 hours

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience <i>(Please print clearly)</i>	COPD Exacerbation	→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	Day Month Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (<i>maximum</i>)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) <i>Please specify</i> _____ ☐ Another condition (eg, condition under study, intercurrent illness) <i>Please specify</i> _____ ☐ Another drug <i>Please specify</i> _____
Corrective Therapy <i>If 'Yes', record details in the COPD Medication or Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Page	365

Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 	SB Receipt Date			
				Day 	Month 	Year 	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	 Day Month Yr			
	 Day Month Yr			
	 Day Month Yr			
	 Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

Day Month Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

Day Month Year

Please PRINT Name

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience <i>(Please print clearly)</i>	COPD Exacerbation	→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) Please specify _____ ☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____ ☐ Another drug Please specify _____
Corrective Therapy <i>If 'Yes', record details in the COPD Medication or Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Page	367

Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 	SB Receipt Date			
				Day	Month	Year	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	 Day Month Yr			
	 Day Month Yr			
	 Day Month Yr			
	 Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

Day	Month	Year

Please PRINT Name

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Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]		

MEDICATION FOR COPD EXACERBATIONS

Has the patient taken any medication for COPD exacerbations since the previous module?							
☐ No ☐ Yes → If 'Yes', please record details below							
Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible) Day Mth Yr	End Date (or if Continuing mark box) Day Mth Yr	
				COPD EXACERBATION	[][][][][][]	[][][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][][]	[][][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][][]	[][][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][][]	[][][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][][]	[][][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][][]	[][][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][][]	[][][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][][]	[][][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][][]	[][][][][][]	☐
For SB							
* For Route, see tab for acceptable abbreviations.							

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Protocol	Centre Number	Patient Number	Patient Initials		
207499/040					

MEDICAL PROCEDURES FOR COPD EXACERBATIONS

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since the previous module?

☐ No

☐ Yes → If 'Yes', please record details below using standard medical terminology

Procedure	Indication	Procedure Start Date			Procedure End Date		
		Day	Mth	Yr	Day	Mth	Yr
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
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	COPD EXACERBATION						
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	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							

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Protocol 207499/040	Centre Number <table border="1"><tr><td></td><td></td><td></td></tr></table>				Patient Number <table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						
0	0	0	0	0													

HEALTHCARE RESOURCE UTILISATION FOR COPD EXACERBATIONS

Complete this form for any **COPD exacerbation related medical care** the patient received since the previous module

Physician Visits (i.e., COPD care excluding scheduled protocol visits)

☐ There were no physician visits since the previous module

Date of Visit				Reason for Visit
Day	Mth	Yr		

Emergency Room (ER)/Urgent Care Visits/Casualty Department Procedures (i.e., lung surgery)

☐ There were no Emergency Room/Urgent Care Visits/Casualty Department Procedures since previous module

Date of Visit Day Mth Yr			Reason for Visit	Patient Admitted from ER?							
				Yes	No						
<table border="1"><tr><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>										☐	☐
<table border="1"><tr><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>										☐	☐
<table border="1"><tr><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>										☐	☐
<table border="1"><tr><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>										☐	☐
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<table border="1"><tr><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>										☐	☐

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Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]		

HEALTHCARE RESOURCE UTILISATION FOR COPD EXACERBATIONS - (cont)

Hospitalisations (also record details of any hospitalisation in the Serious Adverse Experience - COPD Exacerbation section)

☐ There were no hospitalisations since the previous module

Date of Admission Day Mth Yr	Date of Discharge Day Mth Yr	Reason for Admission
[][][][][][]	[][][][][][]	
[][][][][][]	[][][][][][]	
[][][][][][]	[][][][][][]	
[][][][][][]	[][][][][][]	

Intensive Care Unit (ICU) stays (did the patient stay in the ICU during any of the above hospitalisations?)

☐ There were no ICU stays since previous module

Date Admitted to ICU Day Mth Yr	Date Discharged from ICU Day Mth Yr	Reason for ICU Admission
[][][][][][]	[][][][][][]	
[][][][][][]	[][][][][][]	
[][][][][][]	[][][][][][]	
[][][][][][]	[][][][][][]	

Lost Work Days (i.e., days patient missed work due to COPD excluding scheduled protocol visits)

☐ There were no lost work days since the previous module

Stop Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence
[][][][][][]	[][][][][][]	
[][][][][][]	[][][][][][]	
[][][][][][]	[][][][][][]	
[][][][][][]	[][][][][][]	
[][][][][][]	[][][][][][]	
[][][][][][]	[][][][][][]	

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

STUDY CONTINUATION/WITHDRAWAL

Is the patient continuing in the study?

☐ Yes☐ No →*If 'No' please mark the **primary** cause of withdrawal and enter the date of the final visit and the date of the final dose*[1] ☐ Adverse experience (complete AE or SAE section)[2] ☐ Insufficient therapeutic effect[3] ☐ Protocol deviation (including non-compliance)[4] ☐ Lost to follow-up[5] ☐ Other - specify: _____

Date of Final Visit

Day	Month	Yr

Date of Final dose

Day	Month	Yr

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data on this case report form and that all information is complete and accurate.

Investigator's Signature

Date

Day	Month	Yr

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)

SAEs MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS

COMPLETE THE SAE PAGES OPPOSITE

Please complete these pages as fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Experience Course' blank and update it later

SIGN AND DATE THE SAE PAGE**PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE**

- Demography
- Significant Medical/Surgical History and Physical Examination
- Study Medication Record
- Medical Procedures
- Concomitant Medication
- Form D (if applicable)

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE

(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO:

Your local SB CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local SB CRA/Medical monitor within 24 hours

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Protocol	Centre Number	Patient Number	Patient Initials		
207499/040		0 0 0 0 0			

MOD23 & MOD24 - SERIOUS ADVERSE EXPERIENCES

MOD23 & MOD24	Serious Adverse Experiences
MOD23 :	373, 374
MOD24 :	375, 376

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience <i>(Please print clearly)</i>		→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	Day Month Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (<i>maximum</i>)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) Please specify _____ ☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____ ☐ Another drug Please specify _____
Corrective Therapy <i>If 'Yes', record details in the Concomitant Medication or Medical Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Page	374

Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]	SB Receipt Date Day Month Year [][][][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?
☐ No ☐ Yes

Randomisation / Study Medication Number: [][][][][]

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

[][]	[][][]	[][]
Day	Month	Year

Please PRINT Name**SB Medical Monitor's Signature:**

Date

[][]	[][][]	[][]
Day	Month	Year

Please PRINT Name

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Page	375

Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date		
207499/040				Day	Month	Year
		0 0 0 0 0				

SERIOUS ADVERSE EXPERIENCE (SAE)

Person Reporting SAE (Please print clearly) _____		AEGIS Number
Serious Adverse Experience (Please print clearly)		→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	
Outcome If patient died, please complete Form D ←	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) Please specify _____ ☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____ ☐ Another drug Please specify _____
Corrective Therapy If 'Yes', record details in the Concomitant Medication or Medical Procedures section ←	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Page	376

Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]	SB Receipt Date			
				Day [][]	Month [][]	Year [][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	[][][][][][] Day Month Yr			
	[][][][][][] Day Month Yr			
	[][][][][][] Day Month Yr			
	[][][][][][] Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number: [][][][][]

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

[][]	[][]	[][]
Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

[][]	[][]	[][]
Day	Month	Year

Please PRINT Name

Protocol	Centre Number	Patient Number	Patient Initials												
207499/040	<table border="1"><tr><td></td><td></td><td></td></tr></table>				<table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	<table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>				
0	0	0	0	0											

CONFIDENTIAL*PROTOCOL 207499/040**BOOK 9 : VISITS 19 AND 20 (WEEKS 64 AND 68)*

*A MULTICENTRE, OPEN-LABEL EXTENSION STUDY TO EVALUATE
THE SAFETY, TOLERABILITY AND EFFICACY OF ORAL SB 207499
(15mg TWICE DAILY) IN PATIENTS WITH CHRONIC OBSTRUCTIVE
PULMONARY DISEASE (COPD)*

GENERAL INSTRUCTIONS

- Write clearly in capital letters using a black ball point pen and press firmly so that all copies are legible
- Do not write in shaded areas
- Answer ALL questions on every page
- Enter "N/A" if information requested is not available
- Initial and date all changes, additions or deletions. Use a single pen stroke to remove an incorrect entry
- Enter the patient initials on all pages on which information has been entered and the patient number and centre number where required

Do not enter additional data/information after the set of CRF pages has been split/separated

The cover flap or plastic writing board should be used to divide each set of pages before writing on them with a ball point pen

DATE

Please use the following three-letter abbreviations for the months

January	JAN
February	FEB
March	MAR
April	APR
May	MAY
June	JUN
July	JUL
August	AUG
September	SEP
October	OCT
November	NOV
December	DEC

e.g.

0	1	J	A	N	9	9
Day		Month			Year	

 = 1st January 1999

TIME

Unless specified otherwise, please use the 24 hour clock

e.g.

1	5	3	0
24hr:min			

 = 3.30 p.m

PATIENT INITIALS

Please use the following format:

e.g.

ROUTE KEY FOR PRIOR/CONCOMITANT MEDICATION PAGE

PO = By mouth	SL = Sublingual	TD = Transdermal
IV = Intravenous	IT = Intrathecal	IH = Inhaled
IM = Intramuscular	VA = Vaginal	SC = Subcutaneous
IAR = Intra-arterial	NA = Nasal	PR = Rectal
TO = Topical	IA = Intra-articular injection	ID = Intradermal

**SUMMARY CHART OF STUDY PROCEDURES (OPEN BOXES)
PROTOCOL SB 207499/040**

Mark open boxes to confirm that each procedure has been completed.

Procedures	Visit 19	Visit 20
	Week 64	Week 68
Signed written informed consent		
Study Medication compliance		
Concomitant Medication		
Diary Card Review ⁷		
Adverse Experiences ⁸		
COPD Exacerbation assessment/Healthcare Ut.		
Physical (Including Respiratory) Examination		
Resting 12-Lead ECG		
Vital Signs (BP, HR) ³		
Overall Breathlessness (Modified Borg)		
Exercise Tolerance Test - 6 Minute Walk		
Post Exercise Breathlessness		
Pulmonary Function Tests ⁴		
Laboratory Tests ⁵		
Pregnancy Test ⁶		
Quality of Life Assessment: SGRQ		
Quality of Life Assessment: SF-36		
Dispense or re-dispense Open-Label Medication		
Study Continuation / Withdrawal		

³ *Orthostatic blood pressure and heart rate are measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal.*

⁴ *To include FEV₁, FEV₆, FVC, FEF₂₅₋₇₅, FEF₇₅, and PEFR.*

⁵ *Faecal occult blood is measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal. Baseline measure is taken from last FOB in Study 042 or Study 091*

⁶ *Serum pregnancy test for female patients of child bearing potential. Urine test only is done at Follow-Up Visit.*

⁷ *A Diary Card is issued at each visit. The patient will use the Diary Card to record if they feel different since the previous visit.*

⁸ *Patients will be assessed for GI AEs at every visit.*

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Protocol	Centre Number	Patient Number	Patient Initials		
207499/040		0 0 0 0 0			

MODULE 25

Please do not split modules

Module 25 : Visit 19 (Week 64) and Visit 20 (Week 68), Adverse Experiences, Conmeds, Medical Procedures, COPD Exacerbations, Resource Utilisation, Continuation/ Withdrawal

CRF Pages 377 - 416

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

None

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Page 377

Protocol 207499/040	Centre Number	Patient Number	Patient Initials	Visit Date			Visit 19 Week 64
				Day	Month	Year	

PRESENTATION TO CLINIC

Record time of presentation to clinic

24hr:min

Note: Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.

Record the date and time of the patient's last dose of short-acting beta₂ agonist

Day Month Yr 24hr:min
Record the date and time of the patient's last dose of long-acting beta₂ agonist

Day Month Yr 24hr:min

Record the date and time of the patient's last dose of anticholinergic

Day Month Yr 24hr:min

Has the patient smoked within the past 2 hours?

☐ No☐ Yes → If 'Yes' please record time

24hr:min
COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	 Day Month Yr	 Day Month Yr	 Day Month Yr	 Day Month Yr
Level of exacerbation (maximum intensity)	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.

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Page	378

Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 19 Week 64

RESOURCE UTILISATION FOR COPD EXACERBATIONS

If the patient has received any COPD exacerbation related medical care since the previous visit, please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

*Review the diary card for illegible/incomplete entries **in the presence of the patient***

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD Exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 19 Week 64

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	

Date and time of last dose of study medication prior to the study visit

[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70	[][]	[][]	[][]	[][]	[][][]

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance $\geq 80\%$ and $\leq 120\%$?

☐ No →

If 'No' please check the % compliance at the previous visit. If compliance was not $\geq 80\%$ and $\leq 120\%$ at the last visit, please withdraw the patient. Please complete the assessments for Visit 19 and the assessments for patients withdrawing or stopping the study at Visit 19, contained at the end of this visit.

☐ Yes

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 19 Week 64

SMOKING STATUS

Does the patient currently smoke?

☐ No☐ Yes → If 'Yes' please record the average number of cigarettes per day : [][]**PULMONARY REHABILITATION PROGRAMME**

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit?

☐ No☐ Yes**LABORATORY TESTS**

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential). Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date

[][]	[][]	[][]
Day	Month	Yr

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below

Attach label here

Are there any **clinically significant worsenings** since the previous visit?☐ No
☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module

Place the Quest laboratory report in the plastic wallet at the back of this module

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][][]		Visit 19 Week 64

URINALYSIS

Please perform urinalysis using the dipstick provided by Quest and record the results in the patient notes.

Urine Sample Date

[][]	[][]	[][]
Day	Month	Yr

Are the dipstick results negative?

☐

No →

If 'No' please send the sample to Quest for microscopy☐

Yes

Are there any **clinically significant worsenings** since the previous visit on the Quest report?☐

No

☐

Yes →

*If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.***PREGNANCY TEST**

Is the patient a female of child-bearing potential?

☐

No

☐

Yes →

If 'Yes' please request a pregnancy test on the Quest requisition form.

Is the patient pregnant?

☐

No

☐

Yes →

If 'Yes' please withdraw the patient from the study, enter details in the Adverse Experience section. Complete the Early Withdrawal Visit (found in a separate book).

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OVERALL BREATHLESSNESS ASSESSMENT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 19 Week 64

INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed: [][] / [][] / [][]
Day Month Yr

Were any clinically significant changes noted since the last visit?

☐ No

☐ Yes → ☐ Improvement

☐ Worsening →

Enter details in the Adverse Experience section at the back of this module.

Place the ECG trace in the plastic wallet at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 19 Week 64
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PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and/or anticholinergic medications and/or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

STUDY MEDICATION LABEL

Issue the patient one bottle of open-label study medication (70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

Attach study medication
label here

Give the patient the first dose of study medication with food and record the date and time of administration below.

Date and time of administration

Day	Month	Yr	24hr	:	min		

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INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐ No →

If 'No' please complete the assessments for Visit 19 and the Assessments for Patients Withdrawing or Stopping the Study at Visit 19 contained on the following pages. Complete and fax the Withdrawal Form contained in the Withdrawal and Follow-Up Book.

☐ Yes →

If 'Yes' please:

- *Issue a new diary card. Remind the patient to record if they feel differently since starting the study*
- *Ask the patient to return for the next visit in 28 + / - 6 days.*
- **Remind the patient:**
 - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*
 - ii **not** *to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*
 - iii *to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonists (long-acting) for **12 hours** before the next visit.*
 - iv *to refrain from smoking for **2 hours** immediately preceding the visit.*
 - v *to bring back at the next visit any remaining study medication or study medication containers and the diary card.*
 - vi *to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.*

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 19 Week 64

ASSESSMENTS FOR PATIENTS WITHDRAWING OR STOPPING THE STUDY

Complete the assessments below only for patients who are withdrawing early from the study or stopping the study because the product has been registered or because the sponsor has terminated the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes →

If 'Yes' record details in the Adverse Experience section at the back of this module.

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FAECAL OCCULT BLOOD TEST

Issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-Up Visit.

VITAL SIGNS - ORTHOSTATIC CHANGE**1st Measurement: After 5 Minutes Supine**

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

Are there any clinically significant worsenings since the previous assessment?

☐ No

☐ Yes → If 'Yes' record details in the Adverse Experience section at the back of this module.

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Follow-Up Visit in 7 +/- 3 days.

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 	Visit Date			Visit 20 Week 64
				Day 	Month 	Year 	

PRESENTATION TO CLINIC

Record time of presentation to clinic

24hr:min

Note: Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.

Record the date and time of the patient's last dose of short-acting beta₂ agonist

Day Month Yr 24hr:min
Record the date and time of the patient's last dose of long-acting beta₂ agonist

Day Month Yr 24hr:min

Record the date and time of the patient's last dose of anticholinergic

Day Month Yr 24hr:min

Has the patient smoked within the past 2 hours?

☐ No☐ Yes → If 'Yes' please record time

24hr:min
COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	 Day Month Yr	 Day Month Yr	 Day Month Yr	 Day Month Yr
Level of exacerbation (maximum intensity)	☐ Level 1	☐ Level 1	☐ Level 1	☐ Level 1
	☐ Level 2	☐ Level 2	☐ Level 2	☐ Level 2
	☐ Level 3	☐ Level 3	☐ Level 3	☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.

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RESOURCE UTILISATION FOR COPD EXACERBATIONS

Please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

Review the diary card for illegible/incomplete entries **in the presence of the patient**

ADVERSE EXPERIENCES

Please complete the Adverse Experience section at the back of this module. If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

Please complete the Concomitant Medication section at the back of this module. If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD Exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 20 Week 64

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)
[][][][][][]	[][][][][][]	[]	
[][][][][][]	[][][][][][]	[]	
[][][][][][]	[][][][][][]	[]	

Date and time of last dose of study medication prior to the study visit

[][]	[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:	min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70	[][]	[][]	[][]	[][]	[][][]

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance $\geq 80\%$ and $\leq 120\%$?

☐ No →

If 'No' please check the % compliance at the previous visit. If compliance was not $\geq 80\%$ and $\leq 120\%$ at the last visit, please withdraw the patient. Please complete the assessments for Visit 20 and the assessments for patients withdrawing or stopping the study at Visit 20, contained at the end of this visit.

☐ Yes

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 20 Week 64

SMOKING STATUS

Does the patient currently smoke?

☐ No☐ Yes → If 'Yes' please record the average number of cigarettes per day : [][]**PULMONARY REHABILITATION PROGRAMME**

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit?

☐ No☐ Yes**LABORATORY TESTS**

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential). Please refer to the instructions on the SBCL shipping form and manual.

Blood Sample Date

[][]	[][]	[][]
Day	Month	Yr

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below

Attach label here

Are there any **clinically significant worsenings** since the previous visit?☐ No☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module

Place the SBCL laboratory report in the plastic wallet at the back of this module

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 20 Week 64

URINALYSIS

Please perform urinalysis using the dipstick provided by SBCL and record the results in the patient notes.

Urine Sample Date

Day	Month	Yr		

Are the dipstick results negative?

- ☐ No → If 'No' please send the sample to SBCL for microscopy
- ☐ Yes

Are there any **clinically significant worsenings** since the previous visit on the SBCL report?

- ☐ No
- ☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

PREGNANCY TEST

Is the patient a female of child-bearing potential?

- ☐ No
- ☐ Yes → If 'Yes' please request a pregnancy test on the SBCL requisition form.

Is the patient pregnant?

- ☐ No
- ☐ Yes → If 'Yes' please withdraw the patient from the study, enter details in the Adverse Experience section. Complete the Early Withdrawal Visit (found in a separate book).

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OVERALL BREATHLESSNESS ASSESSMENT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 20 Week 64

INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed: [][] / [][] / [][]
Day Month Yr

Were any clinically significant changes noted since the last visit?

☐ No

☐ Yes → ☐ Improvement

☐ Worsening →

Enter details in the Adverse Experience section at the back of this module.

Place the ECG trace in the plastic wallet at the back of this module.

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Protocol		Patient Number	Patient Initials		Visit 20 Week 64
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PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and/or anticholinergic medications and/or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

STUDY MEDICATION LABEL

Issue the patient one bottle of open-label study medication (70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

**Attach study medication
label here**

Give the patient the first dose of study medication with food and record the date and time of administration below.

Date and time of administration

Day	Month	Yr	24hr:	min			

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][][]		Visit 20 Week 64

INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐ No →

If 'No' please complete the assessments for Visit 20 and the Assessments for Patients Withdrawing or Stopping the Study at Visit 20 contained on the following pages. Complete and fax the Withdrawal Form contained in the Withdrawal and Follow-Up Book.

☐ Yes →

If 'Yes' please:

- *Issue a new diary card. Remind the patient to record if they feel differently since starting the study*
- *Ask the patient to return for the next visit in 28 +/- 6 days.*
- *Complete the Study Continuation / Withdrawal page at the back of this module.*
- **Remind the patient:**
 - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*
 - ii **not** *to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*
 - iii *to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonists (long-acting) for **12 hours** before the next visit.*
 - iv *to refrain from smoking for **2 hours** immediately preceding the visit.*
 - v *to bring back at the next visit any remaining study medication or study medication containers and the diary card.*
 - vi *to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.*

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 20 Week 64

ASSESSMENTS FOR PATIENTS WITHDRAWING OR STOPPING THE STUDY

Complete the assessments below only for patients who are withdrawing early from the study or stopping the study because the product has been registered or because the sponsor has terminated the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a clinically significant worsening in the patient's physical condition since the previous examination?

☐ No

☐ Yes →

If 'Yes' record details in the Adverse Experience section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 20 Week 64

FAECAL OCCULT BLOOD TEST

Issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-Up Visit.

VITAL SIGNS - ORTHOSTATIC CHANGE**1st Measurement: After 5 Minutes Supine**

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the previous assessment?

☐ No

☐ Yes → If 'Yes' record details in the Adverse Experience section at the back of this module.

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Follow-Up Visit in 7 +/- 3 days.

ADVERSE EXPERIENCES (Non-serious)**DEFINITIONS****INTENSITY (Maximum)**

MILD	<i>Adverse experience which is easily tolerated</i>
MODERATE	<i>Adverse experience sufficiently discomforting to interfere with daily activities</i>
SEVERE	<i>Adverse experience which prevents normal everyday activities</i>

RELATIONSHIP TO INVESTIGATIONAL DRUG

NOT RELATED	<i>The adverse experience is definitely not related to the test drug</i>
UNLIKELY	<i>There are other more likely causes and the drug is not suspected as a cause</i>
SUSPECTED (REASONABLE POSSIBILITY)	<i>A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug</i>
PROBABLE	<i>There probably is a direct cause and effect relationship between the adverse experience and the study drug</i>

SERIOUS ADVERSE EXPERIENCE (SAE)

An SAE is any event which is :-

- 1 - fatal
- 2 - life threatening
- 3 - disabling/incapacitating
- 4 - results in hospitalisation (excluding elective surgery or routine clinical procedures)
- 5 - prolongs a hospital stay
- 6 - associated with congenital abnormality
- 7 - cancer
- 8 - associated with overdose
- 9 - In addition any event which the investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the the use of the drug should be reported as a serious event

IF AN SAE OCCURS, PLEASE GO TO SAE SECTION IMMEDIATELY AND FOLLOW THE INSTRUCTIONS GIVEN THERE

Use each form for a maximum of two experiences

PLEASE REMEMBER ALL QUESTIONS ON ADVERSE EXPERIENCES FORM SHOULD BE COMPLETED

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Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous module?" Provide the diagnosis, **not** symptoms, where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbations section

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no adverse experiences occurred since the previous module, please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous module?" Provide the diagnosis, **not** symptoms, where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbations section

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no further adverse experiences or changes in adverse experiences occurred since the previous module, please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous module?" Provide the diagnosis, **not** symptoms, where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbations section

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no further adverse experiences or changes in adverse experiences occurred since the previous module, please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the previous module.
(Please write using BLOCK CAPITALS).

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

☐ No concomitant medication changes since the previous module

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experience section using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the new start and end date.

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)			
					Day	Mth	Yr	Day	Mth	Yr	
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* For Route, see tab for acceptable abbreviations.											

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

CONCOMITANT MEDICATION - Continued

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experience section using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the new start and end date.

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in ab- sence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)			
					Day	Mth	Yr	Day	Mth	Yr	
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* For Route, see tab for acceptable abbreviations.

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Protocol	Centre Number	Patient Number	Patient Initials		
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MEDICAL PROCEDURES - (Excluding treatment for COPD Exacerbations)

Do not record procedures used to treat COPD exacerbations here, record them in the COPD Exacerbations section.

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed since the previous module?

☐ No

☐ Yes → If 'Yes', please record details below using standard medical terminology (Please print clearly)

All indications for procedures should be recorded in the Adverse Experience section

Procedure	Indication	Procedure Start Date			Procedure End Date		
		Day	Mth	Yr	Day	Mth	Yr
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SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number	Patient Initials		
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*An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.*

*All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since the previous module please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome If patient died, STOP: go to the COPD SAE section and follow instructions given there	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____ Date : Day Month Yr		

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.

All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages**

If no further COPD exacerbations or changes to COPD exacerbations have occurred since the previous module please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome If patient died, STOP: go to the COPD SAE section and follow instructions given there ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.

All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages**

If no further COPD exacerbations or changes to COPD exacerbations have occurred since the previous module please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome If patient died, STOP: go to the COPD SAE section and follow instructions given there ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)**SAEs MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS****COMPLETE THE SAE PAGES OPPOSITE**

Please complete these pages as fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Experience Course' blank and update it later

SIGN AND DATE THE SAE PAGE**PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE**

- Demography
- Significant Medical/Surgical History and Physical Examination
- Study Medication Record
- Concomitant Medication
- Form D (if applicable)

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE
(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO:

Your local SB CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local SB CRA/Medical monitor within 24 hours

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Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date		
				Day	Month	Year
207499/040		0 0 0 0 0				

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience <i>(Please print clearly)</i>	COPD Exacerbation	→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	Day Month Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) <i>Please specify</i> _____ ☐ Another condition (eg, condition under study, intercurrent illness) <i>Please specify</i> _____ ☐ Another drug <i>Please specify</i> _____
Corrective Therapy <i>If 'Yes', record details in the COPD Medication or Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]	SB Receipt Date			
				Day [][]	Month [][]	Year [][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	[][] [][] [][] Day Month Yr			
	[][] [][] [][] Day Month Yr			
	[][] [][] [][] Day Month Yr			
	[][] [][] [][] Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number: [][][][][]

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

[][]	[][]	[][]
Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

[][]	[][]	[][]
Day	Month	Year

Please PRINT Name

Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date		
				Day	Month	Year
207499/040						

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience <i>(Please print clearly)</i>	COPD Exacerbation	→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	 Day Month Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) <i>Please specify _____</i> ☐ Another condition (eg, condition under study, intercurrent illness) <i>Please specify _____</i> ☐ Another drug <i>Please specify _____</i>
Corrective Therapy <i>If 'Yes', record details in the COPD Medication or Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][][]	SB Receipt Date			
				Day [][]	Month [][]	Year [][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	[][] [][] [][] Day Month Yr			
	[][] [][] [][] Day Month Yr			
	[][] [][] [][] Day Month Yr			
	[][] [][] [][] Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

[][][][][]

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

[][]	[][]	[][]
Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

[][]	[][]	[][]
Day	Month	Year

Please PRINT Name

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Protocol 207499/040	Centre Number <table border="1"><tr><td></td><td></td><td></td></tr></table>				Patient Number <table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						
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MEDICATION FOR COPD EXACERBATIONSHas the patient taken any medication for **COPD exacerbations** since the previous module?☐ No☐ Yes → If 'Yes', please record details below

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)			
					Day	Mth	Yr	Day	Mth	Yr	
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
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				COPD EXACERBATION							☐
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				COPD EXACERBATION							☐
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* For Route, see tab for acceptable abbreviations.											

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MEDICAL PROCEDURES FOR COPD EXACERBATIONS

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since the previous module?

☐ No

☐ Yes → If 'Yes', please record details below using standard medical terminology

Procedure	Indication	Procedure Start Date			Procedure End Date		
		Day	Mth	Yr	Day	Mth	Yr
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
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Protocol 207499/040	Centre Number <table border="1"><tr><td></td><td></td><td></td></tr></table>				Patient Number <table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						
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HEALTHCARE RESOURCE UTILISATION FOR COPD EXACERBATIONS

Complete this form for any **COPD exacerbation related medical care** the patient received since the previous module

Physician Visits (i.e., COPD care excluding scheduled protocol visits)

☐ There were no physician visits since the previous module

Date of Visit Day Mth Yr	Reason for Visit						
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Emergency Room (ER)/Urgent Care Visits/Casualty Department Procedures (i.e., lung surgery)

☐ There were no Emergency Room/Urgent Care Visits/Casualty Department Procedures since previous module

Date of Visit Day Mth Yr	Reason for Visit	Patient Admitted from ER?							
		Yes	No						
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HEALTHCARE RESOURCE UTILISATION FOR COPD EXACERBATIONS - (cont)

Hospitalisations (also record details of any hospitalisation in the Serious Adverse Experience - COPD Exacerbation section)

☐ There were no hospitalisations since the previous module

Date of Admission Day Mth Yr	Date of Discharge Day Mth Yr	Reason for Admission

Intensive Care Unit (ICU) stays (did the patient stay in the ICU during any of the above hospitalisations?)

☐ There were no ICU stays since previous module

Date Admitted to ICU Day Mth Yr	Date Discharged from ICU Day Mth Yr	Reason for ICU Admission

Lost Work Days (i.e., days patient missed work due to COPD excluding scheduled protocol visits)

☐ There were no lost work days since the previous module

Stop Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

STUDY CONTINUATION/WITHDRAWAL

Is the patient continuing in the study?

☐ Yes☐ No →

*If 'No' please mark the **primary** cause of withdrawal and enter the date of the final visit and the date of the final dose*

[1] ☐ Adverse experience (complete AE or SAE section)[2] ☐ Insufficient therapeutic effect[3] ☐ Protocol deviation (including non-compliance)[4] ☐ Lost to follow-up[5] ☐ Other - specify: _____

Date of Final Visit

Day	Month	Yr

Date of Final dose

Day	Month	Yr

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data on this case report form and that all information is complete and accurate.

Investigator's Signature

Date

Day	Month	Yr

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)

SAEs MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS

COMPLETE THE SAE PAGES OPPOSITE

Please complete these pages as fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Experience Course' blank and update it later

SIGN AND DATE THE SAE PAGE**PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE**

- Demography
- Significant Medical/Surgical History and Physical Examination
- Study Medication Record
- Medical Procedures
- Concomitant Medication
- Form D (if applicable)

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE

(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO:

Your local SB CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local SB CRA/Medical monitor within 24 hours

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Protocol	Centre Number	Patient Number	Patient Initials		
207499/040		0 0 0 0 0			

MOD26 & MOD27 - SERIOUS ADVERSE EXPERIENCES

MOD26 & MOD27	Serious Adverse Experiences
MOD26 :	417, 418
MOD27 :	419, 420

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience <i>(Please print clearly)</i>		→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	Day Month Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) Please specify _____ ☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____ ☐ Another drug Please specify _____
Corrective Therapy <i>If 'Yes', record details in the Concomitant Medication or Medical Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Page	418

Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]	SB Receipt Date Day Month Year [][][][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number: [][][][][]

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

[][]	[][][]	[][]
Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

[][]	[][][]	[][]
Day	Month	Year

Please PRINT Name

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience <i>(Please print clearly)</i>		→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	Day Month Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) Please specify _____ ☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____ ☐ Another drug Please specify _____
Corrective Therapy <i>If 'Yes', record details in the Concomitant Medication or Medical Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Page	420

Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]	SB Receipt Date Day Month Year [][][][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number: [][][][][]

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

Day	Month	Year

Please PRINT Name

Protocol	Centre Number	Patient Number	Patient Initials
207499/040		0 0 0 0 0	

CONFIDENTIAL*PROTOCOL 207499/040**BOOK 10 : VISITS 21 AND 22 (WEEKS 72 AND 76)*

*A MULTICENTRE, OPEN-LABEL EXTENSION STUDY TO EVALUATE
THE SAFETY, TOLERABILITY AND EFFICACY OF ORAL SB 207499
(15mg TWICE DAILY) IN PATIENTS WITH CHRONIC OBSTRUCTIVE
PULMONARY DISEASE (COPD)*

DATE

Please use the following three-letter abbreviations for the months

January	JAN
February	FEB
March	MAR
April	APR
May	MAY
June	JUN
July	JUL
August	AUG
September	SEP
October	OCT
November	NOV
December	DEC

e.g.

0	1
Day	

J	A	N
Month		

9	9
Year	

 = 1st January 1999

TIME

Unless specified otherwise, please use the 24 hour clock

e.g.

1	5	3	0

 = 3.30 p.m.

PATIENT INITIALS

Please use the following format:

e.g. [REDACTED]

ROUTE KEY FOR PRIOR/CONCOMITANT MEDICATION PAGE

<i>PO</i>	=	<i>By mouth</i>	<i>SL</i>	=	<i>Sublingual</i>	<i>TD</i>	=	<i>Transdermal</i>
<i>IV</i>	=	<i>Intravenous</i>	<i>IT</i>	=	<i>Intrathecal</i>	<i>IH</i>	=	<i>Inhaled</i>
<i>IM</i>	=	<i>Intramuscular</i>	<i>VA</i>	=	<i>Vaginal</i>	<i>SC</i>	=	<i>Subcutaneous</i>
<i>IAR</i>	=	<i>Intra-arterial</i>	<i>NA</i>	=	<i>Nasal</i>	<i>PR</i>	=	<i>Rectal</i>
<i>TO</i>	=	<i>Topical</i>	<i>IA</i>	=	<i>Intra-articular injection</i>	<i>ID</i>	=	<i>Intradermal</i>

SUMMARY CHART OF STUDY PROCEDURES (OPEN BOXES) PROTOCOL SB 207499/040

Mark open boxes to confirm that each procedure has been completed.

Procedures	Visit 21	Visit 22
	Week 72	Week 76
Signed written informed consent		
Study Medication compliance		
Concomitant Medication		
Diary Card Review ⁷		
Adverse Experiences ⁸		
COPD Exacerbation assessment/Healthcare Ut.		
Physical (Including Respiratory) Examination		
Resting 12-Lead ECG		
Vital Signs (BP, HR) ³		
Overall Breathlessness (Modified Borg)		
Exercise Tolerance Test - 6 Minute Walk		
Post Exercise Breathlessness		
Pulmonary Function Tests ⁴		
Laboratory Tests ⁵		
Pregnancy Test ⁶		
Quality of Life Assessment: SGRQ		
Quality of Life Assessment: SF-36		
Dispense or re-dispense Open-Label Medication		
Study Continuation / Withdrawal		

³ **Orthostatic blood pressure and heart rate are measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal.**

⁴ **To include FEV₁, FEV₆, FVC, FEF₂₅₋₇₅, FEF₇₅, and PEFR.**

⁵ **Faecal occult blood is measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal. Baseline measure is taken from last FOB in Study 042 or Study 091**

⁶ **Serum pregnancy test for female patients of child bearing potential. Urine test only is done at Follow-Up Visit.**

⁷ **A Diary Card is issued at each visit. The patient will use the Diary Card to record if they feel different since the previous visit.**

⁸ **Patients will be assessed for GI AEs at every visit.**



Protocol	Centre Number	Patient Number	Patient Initials		
207499/040		0 0 0 0 0			

MODULE 28

Please do not split modules

Module 28 : Visit 21 (Week 72) and Visit 22 (Week 76), Adverse Experiences, Conmeds, Medical Procedures, COPD Exacerbations, Resource Utilisation, Continuation/ Withdrawal

CRF Pages 421 - 462

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

Visit 21 :
SGRQ
SF36

Protocol	Centre Number	Patient Number	Patient Initials	Visit Date	Visit 21 Week 72
207499/040		0 0 0 0 0		Day Month Year	

PRESENTATION TO CLINIC

Record time of presentation to clinic

24hr:min

Note: *Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.*

Record the date and time of the patient's last dose of short-acting beta₂ agonist

Day	Month	Yr	24hr:min

Record the date and time of the patient's last dose of long-acting beta₂ agonist

Day	Month	Yr	24hr:min

Record the date and time of the patient's last dose of anticholinergic

Day	Month	Yr	24hr:min

Has the patient smoked within the past 2 hours?

☐ No☐ Yes → If 'Yes' please record time

24hr:min
ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

Protocol		Patient Number	Patient Initials		Visit 21 Week 72
207499/040		0 0 0 0 0			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of exacerbation (maximum intensity)	☐ Level 1	☐ Level 1	☐ Level 1	☐ Level 1
	☐ Level 2	☐ Level 2	☐ Level 2	☐ Level 2
	☐ Level 3	☐ Level 3	☐ Level 3	☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.

Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						Visit 21 Week 72

RESOURCE UTILISATION FOR COPD EXACERBATIONS

If the patient has received any COPD exacerbation related medical care since the previous visit, please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

*Review the diary card for illegible/incomplete entries **in the presence of the patient***

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD Exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes →

If 'Yes' record details in the Adverse Experience section at the back of this module.

Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 21 Week 72

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)
[][][][][][]	[][][][][][]	[]	
[][][][][][]	[][][][][][]	[]	
[][][][][][]	[][][][][][]	[]	

Date and time of last dose of study medication prior to the study visit

[][]	[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:min	

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70	[][]	[][]	[][]	[][]	[][][]

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤ 120%?

☐ No →

If 'No' please check the % compliance at the previous visit. If compliance was not ≥ 80% and ≤ 120% at the last visit, please withdraw the patient. Please complete the assessments for Visit 21.

☐ Yes

Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials 		Visit 21 Week 72

SMOKING STATUS

Does the patient currently smoke?

☐ No☐ Yes → If 'Yes' please record the average number of cigarettes per day : **PULMONARY REHABILITATION PROGRAMME**

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit?

☐ No☐ Yes**LABORATORY TESTS***Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential). Please refer to the instructions on the Quest shipping form and manual.*

Blood Sample Date

Day	Month	Yr		

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below

Attach label here

Are there any **clinically significant worsenings** since the previous visit?☐ No☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module**Place the Quest laboratory report in the plastic wallet at the back of this module*

Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials 		Visit 21 Week 72

URINALYSIS

Please perform urinalysis using the dipstick provided by Quest and record the results in the patient notes.

Urine Sample Date

Day	Month	Yr		

Are the dipstick results negative?

- ☐ No → If 'No' please send the sample to Quest for microscopy
- ☐ Yes

Are there any **clinically significant worsenings** since the previous visit on the Quest report?

- ☐ No
- ☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

PREGNANCY TEST

Is the patient a female of child-bearing potential?

- ☐ No
- ☐ Yes → If 'Yes' please request a pregnancy test on the Quest requisition form.

Is the patient pregnant?

- ☐ No
- ☐ Yes → If 'Yes' please withdraw the patient from the study, enter details in the Adverse Experience section. Complete the Early Withdrawal Visit (found in a separate book).

Protocol		Patient Number	Patient Initials		Visit 21 Week 72
207499/040		0 0 0 0 0			

OVERALL BREATHLESSNESS ASSESSMENT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

Protocol		Patient Number	Patient Initials		Visit 21 Week 72
207499/040		0 0 0 0 0			

INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
/	

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed:
Day Month Yr

Were any clinically significant changes noted since the last visit?

☐ No

☐ Yes → ☐ Improvement

☐ Worsening → Enter details in the Adverse Experience section at the back of this module.

Place the ECG trace in the plastic wallet at the back of this module.

Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials 		Visit 21 Week 72

VITAL SIGNS - ORTHOSTATIC CHANGE**1st Measurement: After 5 Minutes Supine**

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min

Are there any **clinically significant worsenings** since the previous assessment?☐ No☐ Yes →

If 'Yes' record details in the Adverse Experience section at the back of this module.

Protocol		Patient Number	Patient Initials		Visit 21 Week 72
207499/040		0 0 0 0 0			

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes. If the patient was too ill to attempt the test, please mark the 'Yes' box and enter 0 for distance walked.

☐ No

☐ Yes → If 'Yes', Distance walked Metres

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

POST-EXERCISE BREATHLESSNESS (Immediately after the patient completes the exercise tolerance)
Heart Rate beats/min
Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

- 0 Nothing at all
- 1 Very, very slight (just noticeable)
- 2 Very slight
- 3 Moderate
- 4 Somewhat severe
- 5 Severe
- 6
- 7 Very severe
- 8
- 9 Very, very severe (almost maximal)
- 10 Maximal

Post-exercise breathlessness score

 .
INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise tolerance test (rest for at least 10 minutes) before performing the pulmonary function tests.

Protocol		Patient Number	Patient Initials		Visit 21 Week 72
207499/040		0 0 0 0 0			

PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and/or anticholinergic medications and/or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

STUDY MEDICATION LABEL

Issue the patient one bottle of open-label study medication (70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

**Attach study medication
label here**

Give the patient the first dose of study medication with food and record the date and time of administration below.

Date and time of administration

Day	Month	Yr	24hr:	min			

Protocol		Patient Number	Patient Initials		Visit 21 Week 72
207499/040		0 0 0 0 0			

INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐ No →

If 'No' please complete the assessments for Visit 21 and issue the patient three Haemoccult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-Up Visit. Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return in 7 +/- 3 days for a Follow-Up Visit.

☐ Yes →

If 'Yes' please:

- *Issue the patient three Haemoccult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the next visit.*
- *Issue a new diary card. Remind the patient to record if they feel differently since starting the study*
- *Ask the patient to return for the next visit in 28 +/- 6 days.*
- **Remind the patient:**
 - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*
 - ii **not** *to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*
 - iii *to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonists (long-acting) for **12 hours** before the next visit.*
 - iv *to refrain from smoking for **2 hours** immediately preceding the visit.*
 - v *to bring back at the next visit any remaining study medication or study medication containers and the diary card.*
 - vi *to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.*

Protocol	Centre Number	Patient Number	Patient Initials	Visit Date	Visit 22 Week 76
207499/040		0 0 0 0 0		Day Month Year	

PRESENTATION TO CLINIC

Record time of presentation to clinic

24hr:min

Note: *Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.*

Record the date and time of the patient's last dose of short-acting beta₂ agonist

Day	Month	Yr	24hr:min

Record the date and time of the patient's last dose of long-acting beta₂ agonist

Day	Month	Yr	24hr:min

Record the date and time of the patient's last dose of anticholinergic

Day	Month	Yr	24hr:min

Has the patient smoked within the past 2 hours?

☐ No☐ Yes → If 'Yes' please record time

24hr:min
COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	 Day Month Yr	 Day Month Yr	 Day Month Yr	 Day Month Yr
Level of exacerbation (maximum intensity)	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.

Protocol		Patient Number	Patient Initials		Visit 22 Week 76
207499/040		0 0 0 0 0			

RESOURCE UTILISATION FOR COPD EXACERBATIONS

Please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

*Review the diary card for illegible/incomplete entries **in the presence of the patient***

ADVERSE EXPERIENCES

Please complete the Adverse Experience section at the back of this module. If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

Please complete the Concomitant Medication section at the back of this module. If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD Exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.

Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials 		Visit 22 Week 76

FAECAL OCCULT BLOOD TEST

Record the results of the faecal occult blood tests performed between visits 21 and 22

Test	Date of Collection Day Mth Yr	Was the faecal occult blood test positive ?
1		☐ No ☐ Yes
2		☐ No ☐ Yes
3		☐ No ☐ Yes

Are these findings clinically significant ?

☐ No

☐ Yes → If 'Yes' record details in the Adverse Experiences section at the back of this module.

Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 22 Week 76

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)
[][][][][][]	[][][][][][]	[]	
[][][][][][]	[][][][][][]	[]	
[][][][][][]	[][][][][][]	[]	

Date and time of last dose of study medication prior to the study visit

[][]	[][][]	[][]	[][]	[][]
Day	Month	Yr	24hr:	min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70	[][]	[][]	[][]	[][]	[][][]

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance $\geq 80\%$ and $\leq 120\%$?

☐

No →

If 'No' please check the % compliance at the previous visit. If compliance was not $\geq 80\%$ and $\leq 120\%$ at the last visit, please withdraw the patient. Please complete the assessments for Visit 22 and the assessments for patients withdrawing or stopping the study at Visit 22, contained at the end of this visit.

☐

Yes

Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials 		Visit 22 Week 76

SMOKING STATUS

Does the patient currently smoke?

☐ No☐ Yes → If 'Yes' please record the average number of cigarettes per day : **PULMONARY REHABILITATION PROGRAMME**

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit?

☐ No☐ Yes**LABORATORY TESTS***Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential). Please refer to the instructions on the Quest shipping form and manual.*

Blood Sample Date

Day	Month	Yr		

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below

Attach label here

Are there any **clinically significant worsenings** since the previous visit?☐ No☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module**Place the Quest laboratory report in the plastic wallet at the back of this module*

Protocol		Patient Number	Patient Initials		Visit 22 Week 76
207499/040		0 0 0 0 0			

URINALYSIS

Please perform urinalysis using the dipstick provided by Quest and record the results in the patient notes.

Urine Sample Date

Day	Month	Yr		

Are the dipstick results negative?

☐ No → If 'No' please send the sample to Quest for microscopy

☐ Yes

Are there any **clinically significant worsenings** since the previous visit on the Quest report?

☐ No

☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

PREGNANCY TEST

Is the patient a female of child-bearing potential?

☐ No

☐ Yes → If 'Yes' please request a pregnancy test on the Quest requisition form.

Is the patient pregnant?

☐ No

☐ Yes → If 'Yes' please withdraw the patient from the study, enter details in the Adverse Experience section. Complete the Early Withdrawal Visit (found in a separate book).

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OVERALL BREATHLESSNESS ASSESSMENT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

Protocol		Patient Number	Patient Initials		Visit 22 Week 76
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INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
/	

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed:
Day Month Yr

Were any clinically significant changes noted since the last visit?

☐ No

☐ Yes → ☐ Improvement

☐ Worsening → Enter details in the Adverse Experience section at the back of this module.

Place the ECG trace in the plastic wallet at the back of this module.

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PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and/or anticholinergic medications and/or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

STUDY MEDICATION LABEL

Issue the patient one bottle of open-label study medication (70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

**Attach study medication
label here**

Give the patient the first dose of study medication with food and record the date and time of administration below.

Date and time of administration

Day	Month	Yr	24hr:min				

Protocol		Patient Number	Patient Initials		Visit 22 Week 76
207499/040		0 0 0 0 0			

INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐ No →

If 'No' please complete the assessments for Visit 22 and the Assessments for Patients Withdrawing or Stopping the Study at Visit 22 contained on the following pages. Complete and fax the Withdrawal Form contained in the Withdrawal and Follow-Up Book.

☐ Yes →

If 'Yes' please:

- *Issue a new diary card. Remind the patient to record if they feel differently since starting the study*
- *Ask the patient to return for the next visit in 28 +/- 6 days.*
- *Complete the Study Continuation / Withdrawal page at the back of this module.*
- **Remind the patient:**
 - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*
 - ii **not** *to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*
 - iii *to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonists (long-acting) for **12 hours** before the next visit.*
 - iv *to refrain from smoking for **2 hours** immediately preceding the visit.*
 - v *to bring back at the next visit any remaining study medication or study medication containers and the diary card.*
 - vi *to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.*

Protocol		Patient Number	Patient Initials		Visit 22 Week 76
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ASSESSMENTS FOR PATIENTS WITHDRAWING OR STOPPING THE STUDY

Complete the assessments below only for patients who are withdrawing early from the study or stopping the study because the product has been registered or because the sponsor has terminated the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a clinically significant worsening in the patient's physical condition since the previous examination?

☐ No☐ Yes

If 'Yes' record details in the Adverse Experience section at the back of this module.

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FAECAL OCCULT BLOOD TEST

Issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-Up Visit.

VITAL SIGNS - ORTHOSTATIC CHANGE**1st Measurement: After 5 Minutes Supine**

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min

Are there any clinically significant worsenings since the previous assessment?

☐ No

☐ Yes → If 'Yes' record details in the Adverse Experience section at the back of this module.

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Follow-Up Visit in 7 +/- 3 days.

ADVERSE EXPERIENCES (Non-serious)**DEFINITIONS****INTENSITY (Maximum)**

MILD	Adverse experience which is easily tolerated
MODERATE	Adverse experience sufficiently discomforting to interfere with daily activities
SEVERE	Adverse experience which prevents normal everyday activities

RELATIONSHIP TO INVESTIGATIONAL DRUG

NOT RELATED	The adverse experience is definitely not related to the test drug
UNLIKELY	There are other more likely causes and the drug is not suspected as a cause
SUSPECTED (REASONABLE POSSIBILITY)	A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug
PROBABLE	There probably is a direct cause and effect relationship between the adverse experience and the study drug

SERIOUS ADVERSE EXPERIENCE (SAE)

An SAE is any event which is :-

- 1 - fatal
- 2 - life threatening
- 3 - disabling/incapacitating
- 4 - results in hospitalisation (excluding elective surgery or routine clinical procedures)
- 5 - prolongs a hospital stay
- 6 - associated with congenital abnormality
- 7 - cancer
- 8 - associated with overdose
- 9 - In addition any event which the investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug should be reported as a serious event

IF AN SAE OCCURS, PLEASE GO TO SAE SECTION IMMEDIATELY AND FOLLOW THE INSTRUCTIONS GIVEN THERE

Use each form for a maximum of two experiences

PLEASE REMEMBER ALL QUESTIONS ON ADVERSE EXPERIENCES FORM SHOULD BE COMPLETED

Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous module?" Provide the diagnosis, **not** symptoms, where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbations section

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no adverse experiences occurred since the previous module, please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

Protocol	Centre Number	Patient Number	Patient Initials		
207499/040		0 0 0 0 0			

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous module?" Provide the diagnosis, **not** symptoms, where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbations section

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no further adverse experiences or changes in adverse experiences occurred since the previous module, please sign the form below and mark this box. ☐

Adverse Experience <i>(please print clearly)</i>		
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time <i>(If ongoing please leave blank)</i>	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i>	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent ☐ Constant	☐ Intermittent ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected ☐ Probable
Corrective Therapy <i>If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate</i>	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____ Date : _____		

Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous module?" Provide the diagnosis, **not** symptoms, where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbations section

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no further adverse experiences or changes in adverse experiences occurred since the previous module, please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy <i>If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate</i> ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____ Date : Day Month Yr		

Protocol	Centre Number	Patient Number	Patient Initials		
207499/040					

CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the previous module.
 (Please write using BLOCK CAPITALS).

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

☐ No concomitant medication changes since the previous module

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experience section using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the new start and end date.

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)			
					Day	Mth	Yr	Day	Mth	Yr	
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* For Route, see tab for acceptable abbreviations.

Protocol	Centre Number	Patient Number	Patient Initials		
207499/040		0 0 0 0 0			

CONCOMITANT MEDICATION - Continued

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experience section using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the new start and end date.

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)			
					Day	Mth	Yr	Day	Mth	Yr	
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* For Route, see tab for acceptable abbreviations.

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Do not record procedures used to treat COPD exacerbations here, record them in the COPD Exacerbations section.

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed since the previous module?

☐ No

☐ Yes → If 'Yes', please record details below using standard medical terminology (Please print clearly)

All indications for procedures should be recorded in the Adverse Experience section

Procedure	Indication	Procedure Start Date			Procedure End Date		
		Day	Mth	Yr	Day	Mth	Yr
For SB							
For SB							
For SB							
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For SB							

Protocol	Centre Number	Patient Number	Patient Initials		
207499/040		0 0 0 0 0			

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.
All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages**

If no COPD Exacerbations since the previous module please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to the COPD SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of ☐ Constant episodes	☐ Intermittent → No. of ☐ Constant episodes
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____ Date : Day Month Yr		

Protocol	Centre Number	Patient Number	Patient Initials		
207499/040		0 0 0 0 0			

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.

All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages**

If no further COPD exacerbations or changes to COPD exacerbations have occurred since the previous module please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome If patient died, STOP: go to the COPD SAE section and follow instructions given there ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

Protocol	Centre Number	Patient Number	Patient Initials		
207499/040		0 0 0 0 0			

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.

All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages**

If no further COPD exacerbations or changes to COPD exacerbations have occurred since the previous module please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to the COPD SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____ Date : Day Month Yr		

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)**SAEs MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS****COMPLETE THE SAE PAGES OPPOSITE**

Please complete these pages as fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Experience Course' blank and update it later

SIGN AND DATE THE SAE PAGE**PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE**

- Demography
- Significant Medical/Surgical History and Physical Examination
- Study Medication Record
- Concomitant Medication
- Form D (if applicable)

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE
(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO:

Your local SB CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local SB CRA/Medical monitor within 24 hours

Protocol	Centre Number			Patient Number					Patient Initials				SB Receipt Date		
													Day	Month	Year
207499/040				0	0	0	0	0							

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience <i>(Please print clearly)</i>	COPD Exacerbation	→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	Day Month Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (<i>maximum</i>)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) <i>Please specify</i> _____ ☐ Another condition (eg, condition under study, intercurrent illness) <i>Please specify</i> _____ ☐ Another drug <i>Please specify</i> _____
Corrective Therapy <i>If 'Yes', record details in the COPD Medication or Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	



Protocol 207499/040	Centre Number [][][]	Patient Number 0 0 0 0 0	Patient Initials [][][][]	SB Receipt Date Day Month Year [][][][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)

Relevant Laboratory Data

Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	[][] Day [][] Month [][] Yr			
	[][] Day [][] Month [][] Yr			
	[][] Day [][] Month [][] Yr			
	[][] Day [][] Month [][] Yr			

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

[][][][][]

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

[][] Day [][] Month [][] Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

[][] Day [][] Month [][] Year

Please PRINT Name

Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date		
207499/040				Day	Month	Year
		0 0 0 0 0				

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

Person Reporting SAE (Please print clearly) _____		AEGIS Number
Serious Adverse Experience (Please print clearly)	COPD Exacerbation	→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	
Outcome If patient died, please complete Form D	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) Please specify _____ ☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____ ☐ Another drug Please specify _____
Corrective Therapy If 'Yes', record details in the COPD Medication or Procedures section	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date	
207499/040		0 0 0 0 0		Day Month Year	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)
Relevant Laboratory Data

Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	 Day Month Yr			
	 Day Month Yr			
	 Day Month Yr			
	 Day Month Yr			

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

If applicable, was randomisation code broken at investigational site?

☐

No

☐

Yes

Randomisation / Study Medication Number:

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

 Day	 Month	 Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

 Day	 Month	 Year

Please PRINT Name

Protocol	Centre Number	Patient Number	Patient Initials		
207499/040					

MEDICATION FOR COPD EXACERBATIONS

Has the patient taken any medication for **COPD exacerbations** since the previous module?

☐ No

☐ Yes → *If 'Yes', please record details below*

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)			
					Day	Mth	Yr	Day	Mth	Yr	
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
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				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											

* For Route, see tab for acceptable abbreviations.

Protocol	Centre Number	Patient Number	Patient Initials		
207499/040		0 0 0 0 0			

MEDICAL PROCEDURES FOR COPD EXACERBATIONS

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since the previous module?

☐ No

☐ Yes → If 'Yes', please record details below using standard medical terminology

Procedure	Indication	Procedure Start Date			Procedure End Date		
		Day	Mth	Yr	Day	Mth	Yr
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							



Protocol	Centre Number	Patient Number	Patient Initials		
207499/040		0 0 0 0 0			

[illegible]

Protocol	Centre Number	Patient Number					Patient Initials		
207499/040		0	0	0	0	0			

Hospitalisations (also record details of any hospitalisation in the Serious Adverse Experience - COPD Exacerbation section)

Date of Admission Day Mth Yr			Date of Discharge Day Mth Yr			Reason for Admission

Date Admitted to ICU				Date Discharged from ICU				Reason for ICU Admission
Day	Mth	Yr		Day	Mth	Yr		

[illegible]

Protocol 207499/040	Centre Number <table border="1"><tr><td></td><td></td><td></td></tr></table>				Patient Number <table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						
0	0	0	0	0													

STUDY CONTINUATION/WITHDRAWAL

Is the patient continuing in the study?

☐ Yes☐ No →*If 'No' please mark the **primary** cause of withdrawal and enter the date of the final visit and the date of the final dose*[1] ☐ Adverse experience (complete AE or SAE section)[2] ☐ Insufficient therapeutic effect[3] ☐ Protocol deviation (including non-compliance)[4] ☐ Lost to follow-up[5] ☐ Other - specify: _____

Date of Final Visit

Day Month Yr

Date of Final dose

Day Month Yr**INVESTIGATOR SIGNATURE**

I certify that I have reviewed the data on this case report form and that all information is complete and accurate.

Investigator's Signature _____

Date

Day Month Yr

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)

SAEs MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS

COMPLETE THE SAE PAGES OPPOSITE

Please complete these pages as fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Experience Course' blank and update it later

SIGN AND DATE THE SAE PAGE**PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE**

- Demography
- Significant Medical/Surgical History and Physical Examination
- Study Medication Record
- Medical Procedures
- Concomitant Medication
- Form D (if applicable)

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE

(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO:

Your local SB CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local SB CRA/Medical monitor within 24 hours



Protocol	Centre Number	Patient Number	Patient Initials													
207499/040	<table border="1"><tr><td></td><td></td><td></td></tr></table>				<table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	<table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>					
0	0	0	0	0												

MOD29 & MOD30 - SERIOUS ADVERSE EXPERIENCES

MOD29 & MOD30	Serious Adverse Experiences
MOD29 :	463, 464
MOD30 :	465, 466

Protocol	Centre Number			Patient Number					Patient Initials				SB Receipt Date			
													Day	Month	Year	
207499/040				0	0	0	0	0								

SERIOUS ADVERSE EXPERIENCE (SAE)

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience <i>(Please print clearly)</i>		→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	Day Month Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (<i>maximum</i>)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) <i>Please specify</i> _____ ☐ Another condition (eg, condition under study, intercurrent illness) <i>Please specify</i> _____ ☐ Another drug <i>Please specify</i> _____
Corrective Therapy <i>If 'Yes', record details in the Concomitant Medication or Medical Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	



Protocol 207499/040	Centre Number [][][]	Patient Number 0 0 0 0 0	Patient Initials [][][][]	SB Receipt Date Day Month Year [][][][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data**

Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	[][] Day [][] Month [][] Yr			
	[][] Day [][] Month [][] Yr			
	[][] Day [][] Month [][] Yr			
	[][] Day [][] Month [][] Yr			

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

[][][][][]**Investigator's Signature:**

(confirming that the above data are accurate and complete)

Date

[][]	[][]	[][]
Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

[][]	[][]	[][]
Day	Month	Year

Please PRINT Name

Protocol	Centre Number			Patient Number					Patient Initials				SB Receipt Date			
													Day	Month	Year	
207499/040				0	0	0	0	0								

SERIOUS ADVERSE EXPERIENCE (SAE)

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience <i>(Please print clearly)</i>		→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	Day Month Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (<i>maximum</i>)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) <i>Please specify</i> _____ ☐ Another condition (eg, condition under study, intercurrent illness) <i>Please specify</i> _____ ☐ Another drug <i>Please specify</i> _____
Corrective Therapy <i>If 'Yes', record details in the Concomitant Medication or Medical Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	



Protocol 207499/040	Centre Number [][][]	Patient Number 0 0 0 0 0	Patient Initials [][][][]	SB Receipt Date Day Month Year [][][][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data**

Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	[][][][][][] Day Month Yr			
	[][][][][][] Day Month Yr			
	[][][][][][] Day Month Yr			
	[][][][][][] Day Month Yr			

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

[][][][][]**Investigator's Signature:**

(confirming that the above data are accurate and complete)

Date

[][]	[][][]	[][]
Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

[][]	[][][]	[][]
Day	Month	Year

Please PRINT Name

Protocol	Centre Number	Patient Number	Patient Initials
207499/040		0 0 0 0 0	

CONFIDENTIAL*PROTOCOL 207499/040**BOOK 11 : VISITS 23 AND 24 (WEEKS 80 AND 84)*

***A MULTICENTRE, OPEN-LABEL EXTENSION STUDY TO EVALUATE
THE SAFETY, TOLERABILITY AND EFFICACY OF ORAL SB 207499
(15mg TWICE DAILY) IN PATIENTS WITH CHRONIC OBSTRUCTIVE
PULMONARY DISEASE (COPD)***

GENERAL INSTRUCTIONS

- Write clearly in capital letters using a black ball point pen and press firmly so that all copies are legible
- Do not write in shaded areas
- Answer ALL questions on every page
- Enter "N/A" if information requested is not available
- Initial and date all changes, additions or deletions. Use a single pen stroke to remove an incorrect entry
- Enter the patient initials on all pages on which information has been entered and the patient number and centre number where required
- Do not enter additional data/information after the set of CRF pages has been split/separated
- The cover flap or plastic writing board should be used to divide each set of pages before writing on them with a ball point pen

DATE

Please use the following three-letter abbreviations for the months

January	JAN
February	FEB
March	MAR
April	APR
May	MAY
June	JUN
July	JUL
August	AUG
September	SEP
October	OCT
November	NOV
December	DEC

e.g.

0	1	J	A	N	9	9
Day		Month			Year	

 = 1st January 1999

TIME

Unless specified otherwise, please use the 24 hour clock

e.g.

1	5	3	0
24hr:min			

 = 3.30 p.m

PATIENT INITIALS

Please use the following format:

e.g.

ROUTE KEY FOR PRIOR/CONCOMITANT MEDICATION PAGE

PO = By mouth	SL = Sublingual	TD = Transdermal
IV = Intravenous	IT = Intrathecal	IH = Inhaled
IM = Intramuscular	VA = Vaginal	SC = Subcutaneous
IAR = Intra-arterial	NA = Nasal	PR = Rectal
TO = Topical	IA = Intra-articular injection	ID = Intradermal

**SUMMARY CHART OF STUDY PROCEDURES (OPEN BOXES)
PROTOCOL SB 207499/040**

Mark open boxes to confirm that each procedure has been completed.

Procedures	Visit 23 Week 80	Visit 24 Week 84
Signed written informed consent		
Study Medication compliance		
Concomitant Medication		
Diary Card Review ⁷		
Adverse Experiences ⁸		
COPD Exacerbation assessment/Healthcare Ut.		
Physical (Including Respiratory) Examination		
Resting 12-Lead ECG		
Vital Signs (BP, HR) ³		
Overall Breathlessness (Modified Borg)		
Exercise Tolerance Test - 6 Minute Walk		
Post Exercise Breathlessness		
Pulmonary Function Tests ⁴		
Laboratory Tests ⁵		
Pregnancy Test ⁶		
Quality of Life Assessment: SGRQ		
Quality of Life Assessment: SF-36		
Dispense Open-Label Medication		
Study Continuation / Withdrawal		

³ ***Orthostatic blood pressure and heart rate are measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal.***

⁴ ***To include FEV₁, FEV₆, FVC, FEF₂₅₋₇₅, FEF₇₅, and PEFR.***

⁵ ***Faecal occult blood is measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal. Baseline measure is taken from last FOB in Study 042 or Study 091***

⁶ ***Serum pregnancy test for female patients of child bearing potential. Urine test only is done at Follow-Up Visit.***

⁷ ***A Diary Card is issued at each visit. The patient will use the Diary Card to record if they feel different since the previous visit.***

⁸ ***Patients will be assessed for GI AEs at every visit.***

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Protocol	Centre Number	Patient Number	Patient Initials		
207499/040		0 0 0 0 0			

MODULE 31

Please do not split modules

Module 31 : Visit 23 (Week 80) and Visit 24 (Week 84), Adverse Experiences, Conmeds, Medical Procedures, COPD Exacerbations, Resource Utilisation, Continuation/Withdrawal

CRF Pages 467 - 508

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

None

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Page 467

Protocol 207499/040	Centre Number	Patient Number	Patient Initials	Visit Date			Visit 23 Week 80
				Day	Month	Year	

PRESENTATION TO CLINIC

Record time of presentation to clinic

24hr:min

Note: Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.

Record the date and time of the patient's last dose of short-acting beta₂ agonist

Day Month Yr 24hr:min
Record the date and time of the patient's last dose of long-acting beta₂ agonist

Day Month Yr 24hr:min

Record the date and time of the patient's last dose of anticholinergic

Day Month Yr 24hr:min

Has the patient smoked within the past 2 hours?

☐ No☐ Yes → If 'Yes' please record time

24hr:min
COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	 Day Month Yr	 Day Month Yr	 Day Month Yr	 Day Month Yr
Level of exacerbation (maximum intensity)	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						Visit 23 Week 80

RESOURCE UTILISATION FOR COPD EXACERBATIONS

If the patient has received any COPD exacerbation related medical care since the previous visit, please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

*Review the diary card for illegible/incomplete entries **in the presence of the patient***

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD Exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.

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Page	469

Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 23 Week 80

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	

Date and time of last dose of study medication prior to the study visit

[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70	[][]	[][]	[][]	[][]	[][][]

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance $\geq 80\%$ and $\leq 120\%$?

☐ No →

If 'No' please check the % compliance at the previous visit. If compliance was not $\geq 80\%$ and $\leq 120\%$ at the last visit, please withdraw the patient. Please complete the assessments for Visit 23 and the assessments for patients withdrawing or stopping the study at Visit 23, contained at the end of this visit.

☐ Yes

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Page	470

Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 23 Week 80

SMOKING STATUS

Does the patient currently smoke?

☐ No☐ Yes → If 'Yes' please record the average number of cigarettes per day : [][]**PULMONARY REHABILITATION PROGRAMME**

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit?

☐ No☐ Yes**LABORATORY TESTS**

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential). Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date

[][]	[][]	[][]
Day	Month	Yr

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below

Attach label here

Are there any **clinically significant worsenings** since the previous visit?☐ No
☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module

Place the Quest laboratory report in the plastic wallet at the back of this module

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Page	471

Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 23 Week 80

URINALYSIS

Please perform urinalysis using the dipstick provided by Quest and record the results in the patient notes.

Urine Sample Date

[][]	[][]	[][]
Day	Month	Yr

Are the dipstick results negative?

☐

No →

If 'No' please send the sample to Quest for microscopy☐

Yes

Are there any **clinically significant worsenings** since the previous visit on the Quest report?☐

No

☐

Yes →

*If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.***PREGNANCY TEST**

Is the patient a female of child-bearing potential?

☐

No

☐

Yes →

If 'Yes' please request a pregnancy test on the Quest requisition form.

Is the patient pregnant?

☐

No

☐

Yes →

If 'Yes' please withdraw the patient from the study, enter details in the Adverse Experience section. Complete the Early Withdrawal Visit (found in a separate book).

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OVERALL BREATHLESSNESS ASSESSMENT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 23 Week 80

INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed: [][] [][] [][]
Day Month Yr

Were any clinically significant changes noted since the last visit?

☐ No

☐ Yes → ☐ Improvement

☐ Worsening →

Enter details in the Adverse Experience section at the back of this module.

Place the ECG trace in the plastic wallet at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 23 Week 80

PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and/or anticholinergic medications and/or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

STUDY MEDICATION LABEL

Issue the patient one bottle of open-label study medication (70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

Attach study medication
label here

Give the patient the first dose of study medication with food and record the date and time of administration below.

Date and time of administration

[][]	[][]	[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:	min	

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Protocol		Patient Number	Patient Initials		Visit 23 Week 80
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INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐ No →

If 'No' please complete the assessments for Visit 23 and the Assessments for Patients Withdrawing or Stopping the Study at Visit 23 contained on the following pages. Complete and fax the Withdrawal Form contained in the Withdrawal and Follow-Up Book.

☐ Yes →

If 'Yes' please:

- *Issue a new diary card. Remind the patient to record if they feel differently since starting the study*
- *Ask the patient to return for the next visit in 28 + / - 6 days.*
- **Remind the patient:**
 - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*
 - ii **not** *to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*
 - iii *to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonists (long-acting) for **12 hours** before the next visit.*
 - iv *to refrain from smoking for **2 hours** immediately preceding the visit.*
 - v *to bring back at the next visit any remaining study medication or study medication containers and the diary card.*
 - vi *to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.*

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 23 Week 80

ASSESSMENTS FOR PATIENTS WITHDRAWING OR STOPPING THE STUDY

Complete the assessments below only for patients who are withdrawing early from the study or stopping the study because the product has been registered or because the sponsor has terminated the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a clinically significant worsening in the patient's physical condition since the previous examination?

☐ No

☐ Yes →

If 'Yes' record details in the Adverse Experience section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 23 Week 80

FAECAL OCCULT BLOOD TEST

Issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-Up Visit.

VITAL SIGNS - ORTHOSTATIC CHANGE**1st Measurement: After 5 Minutes Supine**

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the previous assessment?

☐ No

☐ Yes → If 'Yes' record details in the Adverse Experience section at the back of this module.

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Follow-Up Visit in 7 +/- 3 days.

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PRESENTATION TO CLINIC

Record time of presentation to clinic

 24hr:min

Note: *Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.*

Record the date and time of the patient's last dose of short-acting beta₂ agonist

Day	Month	Yr	24hr:min		

Record the date and time of the patient's last dose of long-acting beta₂ agonist

Day	Month	Yr	24hr:min		

Record the date and time of the patient's last dose of anticholinergic

Day	Month	Yr	24hr:min		

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes → If 'Yes' please record time

 24hr:min

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 24 Week 84

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of exacerbation (maximum intensity)	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.

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RESOURCE UTILISATION FOR COPD EXACERBATIONS

Please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

Review the diary card for illegible/incomplete entries in the presence of the patient

ADVERSE EXPERIENCES

Please complete the Adverse Experience section at the back of this module. If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

Please complete the Concomitant Medication section at the back of this module. If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD Exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 24 Week 84

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	

Date and time of last dose of study medication prior to the study visit

[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70	[][]	[][]	[][]	[][]	[][][]

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance $\geq 80\%$ and $\leq 120\%$?

☐ No →

If 'No' please check the % compliance at the previous visit. If compliance was not $\geq 80\%$ and $\leq 120\%$ at the last visit, please withdraw the patient. Please complete the assessments for Visit 24 and the assessments for patients withdrawing or stopping the study at Visit 24, contained at the end of this visit.

☐ Yes

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 24 Week 84

SMOKING STATUS

Does the patient currently smoke?

☐ No☐ Yes → If 'Yes' please record the average number of cigarettes per day : [][]**PULMONARY REHABILITATION PROGRAMME**

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit?

☐ No☐ Yes**LABORATORY TESTS**

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential). Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date

[][]	[][]	[][]
Day	Month	Yr

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below

Attach label here

Are there any **clinically significant worsenings** since the previous visit?☐ No
☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module

Place the Quest laboratory report in the plastic wallet at the back of this module

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][][]		Visit 24 Week 84

URINALYSIS

Please perform urinalysis using the dipstick provided by Quest and record the results in the patient notes.

Urine Sample Date [][][][][][]
 Day Month Yr

Are the dipstick results negative?

- ☐ No → *If 'No' please send the sample to Quest for microscopy*
- ☐ Yes

Are there any **clinically significant worsenings** since the previous visit on the Quest report?

- ☐ No
- ☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

PREGNANCY TEST

Is the patient a female of child-bearing potential?

- ☐ No
- ☐ Yes → *If 'Yes' please request a pregnancy test on the Quest requisition form.*

Is the patient pregnant?

- ☐ No
- ☐ Yes → *If 'Yes' please withdraw the patient from the study, enter details in the Adverse Experience section. Complete the Early Withdrawal Visit (found in a separate book).*

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OVERALL BREATHLESSNESS ASSESSMENT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed: [][][] [][][] [][][]
Day Month Yr

Were any clinically significant changes noted since the last visit?

☐ No

☐ Yes → ☐ Improvement

☐ Worsening →

Enter details in the Adverse Experience section at the back of this module.

Place the ECG trace in the plastic wallet at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 24 Week 84

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes. If the patient was too ill to attempt the test, please mark the 'Yes' box and enter 0 for distance walked.

☐ No

☐ Yes → If 'Yes', Distance walked [][][] Metres

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

POST-EXERCISE BREATHLESSNESS(Immediately after the patient completes the exercise tolerance)

Heart Rate [][][] beats/min

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

- 0 Nothing at all
- 1 Very, very slight (just noticeable)
- 2 Very slight
- 3 Moderate
- 4 Somewhat severe
- 5 Severe
- 6
- 7 Very severe
- 8
- 9 Very, very severe (almost maximal)
- 10 Maximal

Post-exercise breathlessness score

[][]	.	[]

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise tolerance test (rest for at least 10 minutes) before performing the pulmonary function tests.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 24 Week 84

PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and/or anticholinergic medications and/or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

STUDY MEDICATION LABEL

Issue the patient one bottle of open-label study medication (70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

**Attach study medication
label here**

Give the patient the first dose of study medication with food and record the date and time of administration below.

Date and time of administration

[][]	[][]	[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:	min	

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 24 Week 84

INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐ No →

If 'No' please complete the assessments for Visit 24 and the Assessments for Patients Withdrawing or Stopping the Study at Visit 24 contained on the following pages. Complete and fax the Withdrawal Form contained in the Withdrawal and Follow-Up Book.

☐ Yes →

If 'Yes' please:

- Issue a new diary card. Remind the patient to record if they feel differently since starting the study
- Ask the patient to return for the next visit in 28 +/- 6 days.
- Complete the Study Continuation / Withdrawal page at the back of this module.
- **Remind the patient:**
 - i to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.
 - ii **not** to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).
 - iii to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonists (long-acting) for **12 hours** before the next visit.
 - iv to refrain from smoking for **2 hours** immediately preceding the visit.
 - v to bring back at the next visit any remaining study medication or study medication containers and the diary card.
 - vi to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.

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ASSESSMENTS FOR PATIENTS WITHDRAWING OR STOPPING THE STUDY

Complete the assessments below only for patients who are withdrawing early from the study or stopping the study because the product has been registered or because the sponsor has terminated the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a clinically significant worsening in the patient's physical condition since the previous examination?

☐ No

☐ Yes →

If 'Yes' record details in the Adverse Experience section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 24 Week 84

FAECAL OCCULT BLOOD TEST

Issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-Up Visit.

VITAL SIGNS - ORTHOSTATIC CHANGE**1st Measurement: After 5 Minutes Supine**

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the previous assessment?

☐ No

☐ Yes → If 'Yes' record details in the Adverse Experience section at the back of this module.

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Follow-Up Visit in 7 +/- 3 days.

ADVERSE EXPERIENCES (Non-serious)**DEFINITIONS****INTENSITY (Maximum)**

<i>MILD</i>	<i>Adverse experience which is easily tolerated</i>
<i>MODERATE</i>	<i>Adverse experience sufficiently discomforting to interfere with daily activities</i>
<i>SEVERE</i>	<i>Adverse experience which prevents normal everyday activities</i>

RELATIONSHIP TO INVESTIGATIONAL DRUG

<i>NOT RELATED</i>	<i>The adverse experience is definitely not related to the test drug</i>
<i>UNLIKELY</i>	<i>There are other more likely causes and the drug is not suspected as a cause</i>
<i>SUSPECTED (REASONABLE POSSIBILITY)</i>	<i>A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug</i>
<i>PROBABLE</i>	<i>There probably is a direct cause and effect relationship between the adverse experience and the study drug</i>

SERIOUS ADVERSE EXPERIENCE (SAE)

An SAE is any event which is :-

- 1 - fatal
- 2 - life threatening
- 3 - disabling/incapacitating
- 4 - results in hospitalisation (excluding elective surgery or routine clinical procedures)
- 5 - prolongs a hospital stay
- 6 - associated with congenital abnormality
- 7 - cancer
- 8 - associated with overdose
- 9 - In addition any event which the investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug should be reported as a serious event

IF AN SAE OCCURS, PLEASE GO TO SAE SECTION IMMEDIATELY AND FOLLOW THE INSTRUCTIONS GIVEN THERE

Use each form for a maximum of two experiences

PLEASE REMEMBER ALL QUESTIONS ON ADVERSE EXPERIENCES FORM SHOULD BE COMPLETED

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous module?" Provide the diagnosis, **not** symptoms, where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbations section

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no adverse experiences occurred since the previous module, please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous module?" Provide the diagnosis, **not** symptoms, where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbations section

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no further adverse experiences or changes in adverse experiences occurred since the previous module, please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous module?" Provide the diagnosis, **not** symptoms, where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbations section

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no further adverse experiences or changes in adverse experiences occurred since the previous module, please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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Protocol 207499/040	Centre Number <table border="1"><tr><td></td><td></td><td></td></tr></table>				Patient Number <table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						
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CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the previous module.
(Please write using BLOCK CAPITALS).

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

☐ No concomitant medication changes since the previous module

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experience section using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the new start and end date.

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)			
					Day	Mth	Yr	Day	Mth	Yr	
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* For Route, see tab for acceptable abbreviations.											

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Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

CONCOMITANT MEDICATION - Continued

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experience section using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the new start and end date.

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)			
					Day	Mth	Yr	Day	Mth	Yr	
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* For Route, see tab for acceptable abbreviations.											

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Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]		

MEDICAL PROCEDURES - (Excluding treatment for COPD Exacerbations)

Do not record procedures used to treat COPD exacerbations here, record them in the COPD Exacerbations section.

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed since the previous module?

☐ No

☐ Yes → If 'Yes', please record details below using standard medical terminology (Please print clearly)

All indications for procedures should be recorded in the Adverse Experience section

Procedure	Indication	Procedure Start Date			Procedure End Date		
		Day	Mth	Yr	Day	Mth	Yr
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.
All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages**

If no COPD Exacerbations since the previous module please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome If patient died, STOP: go to the COPD SAE section and follow instructions given there ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____ Date : Day Month Yr		

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.

All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages**

If no further COPD exacerbations or changes to COPD exacerbations have occurred since the previous module please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome If patient died, STOP: go to the COPD SAE section and follow instructions given there ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.

All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages**

If no further COPD exacerbations or changes to COPD exacerbations have occurred since the previous module please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome If patient died, STOP: go to the COPD SAE section and follow instructions given there ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)**SAEs MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS****COMPLETE THE SAE PAGES OPPOSITE**

Please complete these pages as fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Experience Course' blank and update it later

SIGN AND DATE THE SAE PAGE**PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE**

- Demography
- Significant Medical/Surgical History and Physical Examination
- Study Medication Record
- Concomitant Medication
- Form D (if applicable)

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE
(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO:

Your local SB CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local SB CRA/Medical monitor within 24 hours

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience <i>(Please print clearly)</i>	COPD Exacerbation	→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	 Day Month Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) <i>Please specify _____</i> ☐ Another condition (eg, condition under study, intercurrent illness) <i>Please specify _____</i> ☐ Another drug <i>Please specify _____</i>
Corrective Therapy <i>If 'Yes', record details in the COPD Medication or Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]	SB Receipt Date Day Month Year [][][][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

[][][][][]

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

[][][]	[][][]	[][][]
Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

[][][]	[][][]	[][][]
Day	Month	Year

Please PRINT Name

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience <i>(Please print clearly)</i>	COPD Exacerbation	→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	 Day Month Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) <i>Please specify</i> _____ ☐ Another condition (eg, condition under study, intercurrent illness) <i>Please specify</i> _____ ☐ Another drug <i>Please specify</i> _____
Corrective Therapy <i>If 'Yes', record details in the COPD Medication or Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]	SB Receipt Date Day Month Year [][][][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	Day Month Yr [][][][][]			
	Day Month Yr [][][][][]			
	Day Month Yr [][][][][]			
	Day Month Yr [][][][][]			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

[][][][][]

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

[][]	[][][]	[][]
Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

[][]	[][][]	[][]
Day	Month	Year

Please PRINT Name

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Protocol 207499/040	Centre Number <table border="1"><tr><td></td><td></td><td></td></tr></table>				Patient Number <table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						
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MEDICATION FOR COPD EXACERBATIONSHas the patient taken any medication for **COPD exacerbations** since the previous module?☐ No☐ Yes → If 'Yes', please record details below

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)			
					Day	Mth	Yr	Day	Mth	Yr	
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
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				COPD EXACERBATION							☐
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				COPD EXACERBATION							☐
For SB											

* For Route, see tab for acceptable abbreviations.

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

MEDICAL PROCEDURES FOR COPD EXACERBATIONS

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since the previous module?

☐ No

☐ Yes → If 'Yes', please record details below using standard medical terminology

Procedure	Indication	Procedure Start Date			Procedure End Date		
		Day	Mth	Yr	Day	Mth	Yr
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
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	COPD EXACERBATION						
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HEALTHCARE RESOURCE UTILISATION FOR COPD EXACERBATIONS

Complete this form for any **COPD exacerbation related medical care** the patient received since the previous module

Physician Visits (i.e., COPD care excluding scheduled protocol visits)

☐ There were no physician visits since the previous module

Date of Visit				Reason for Visit
Day	Mth	Yr		

Emergency Room (ER)/Urgent Care Visits/Casualty Department Procedures (i.e., lung surgery)

☐ There were no Emergency Room/Urgent Care Visits/Casualty Department Procedures since previous module

Date of Visit			Reason for Visit	Patient Admitted from ER?						
				Yes	No					
Day	Mth	Yr								
<table><tr><td></td><td></td><td></td><td></td><td></td></tr></table>									☐	☐
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Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]		

HEALTHCARE RESOURCE UTILISATION FOR COPD EXACERBATIONS - (cont)

Hospitalisations (also record details of any hospitalisation in the Serious Adverse Experience - COPD Exacerbation section)

☐ There were no hospitalisations since the previous module

Date of Admission Day Mth Yr	Date of Discharge Day Mth Yr	Reason for Admission
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	

Intensive Care Unit (ICU) stays (did the patient stay in the ICU during any of the above hospitalisations?)

☐ There were no ICU stays since previous module

Date Admitted to ICU Day Mth Yr	Date Discharged from ICU Day Mth Yr	Reason for ICU Admission
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	

Lost Work Days (i.e., days patient missed work due to COPD excluding scheduled protocol visits)

☐ There were no lost work days since the previous module

Stop Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	

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Protocol 207499/040	Centre Number <table border="1"><tr><td></td><td></td><td></td></tr></table>				Patient Number <table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						
0	0	0	0	0													

STUDY CONTINUATION/WITHDRAWAL

Is the patient continuing in the study?

☐ Yes☐ No →

*If 'No' please mark the **primary** cause of withdrawal and enter the date of the final visit and the date of the final dose*

[1] ☐ Adverse experience (complete AE or SAE section)[2] ☐ Insufficient therapeutic effect[3] ☐ Protocol deviation (including non-compliance)[4] ☐ Lost to follow-up[5] ☐ Other - specify: _____

Date of Final Visit

Day	Month	Yr	

Date of Final dose

Day	Month	Yr	

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data on this case report form and that all information is complete and accurate.

Investigator's Signature

Date

Day	Month	Yr	

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)

SAEs MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS

COMPLETE THE SAE PAGES OPPOSITE

Please complete these pages as fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Experience Course' blank and update it later

SIGN AND DATE THE SAE PAGE**PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE**

- Demography
- Significant Medical/Surgical History and Physical Examination
- Study Medication Record
- Medical Procedures
- Concomitant Medication
- Form D (if applicable)

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE

(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO:

Your local SB CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local SB CRA/Medical monitor within 24 hours

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Protocol	Centre Number	Patient Number	Patient Initials		
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MOD29 & MOD30 - SERIOUS ADVERSE EXPERIENCES

MOD29 & MOD30	Serious Adverse Experiences
MOD29 :	509, 510
MOD30 :	511, 512

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience <i>(Please print clearly)</i>		→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	 Day Month Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) Please specify _____ ☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____ ☐ Another drug Please specify _____
Corrective Therapy <i>If 'Yes', record details in the Concomitant Medication or Medical Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Page	510

Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]	SB Receipt Date Day Month Year [][][][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	Day Month Yr [][][][][]			
	Day Month Yr [][][][][]			
	Day Month Yr [][][][][]			
	Day Month Yr [][][][][]			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

[]	[]	[]	[]	[]

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

[][]	[][]	[][]
Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

[][]	[][]	[][]
Day	Month	Year

Please PRINT Name

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience <i>(Please print clearly)</i>		→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	 Day Month Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) Please specify _____ ☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____ ☐ Another drug Please specify _____
Corrective Therapy <i>If 'Yes', record details in the Concomitant Medication or Medical Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Page	512

Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 	SB Receipt Date			
				Day	Month	Year	

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	 Day Month Yr			
	 Day Month Yr			
	 Day Month Yr			
	 Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

Day Month Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

Day Month Year

Please PRINT Name

Protocol	Centre Number	Patient Number	Patient Initials
207499/040		0 0 0 0 0	

CONFIDENTIAL*PROTOCOL 207499/040**BOOK 12 : VISITS 25 AND 26 (WEEKS 88 AND 92)*

***A MULTICENTRE, OPEN-LABEL EXTENSION STUDY TO EVALUATE
THE SAFETY, TOLERABILITY AND EFFICACY OF ORAL SB 207499
(15mg TWICE DAILY) IN PATIENTS WITH CHRONIC OBSTRUCTIVE
PULMONARY DISEASE (COPD)***

GENERAL INSTRUCTIONS

- Write clearly in capital letters using a black ball point pen and press firmly so that all copies are legible
- Do not write in shaded areas
- Answer ALL questions on every page
- Enter "N/A" if information requested is not available
- Initial and date all changes, additions or deletions. Use a single pen stroke to remove an incorrect entry
- Enter the patient initials on all pages on which information has been entered and the patient number and centre number where required
- Do not enter additional data/information after the set of CRF pages has been split/separated
- The cover flap or plastic writing board should be used to divide each set of pages before writing on them with a ball point pen

DATE

Please use the following three-letter abbreviations for the months

January	JAN
February	FEB
March	MAR
April	APR
May	MAY
June	JUN
July	JUL
August	AUG
September	SEP
October	OCT
November	NOV
December	DEC

e.g.

0	1	J	A	N	9	9
Day		Month			Year	

 = 1st January 1999

TIME

Unless specified otherwise, please use the 24 hour clock

e.g.

1	5	3	0
24hr:min			

 = 3.30 p.m

PATIENT INITIALS

Please use the following format:

e.g.

ROUTE KEY FOR PRIOR/CONCOMITANT MEDICATION PAGE

PO = By mouth	SL = Sublingual	TD = Transdermal
IV = Intravenous	IT = Intrathecal	IH = Inhaled
IM = Intramuscular	VA = Vaginal	SC = Subcutaneous
IAR = Intra-arterial	NA = Nasal	PR = Rectal
TO = Topical	IA = Intra-articular injection	ID = Intradermal

**SUMMARY CHART OF STUDY PROCEDURES (OPEN BOXES)
PROTOCOL SB 207499/040**

Mark open boxes to confirm that each procedure has been completed.

Procedures	Visit 25 Week 88	Visit 26 Week 92
Signed written informed consent		
Study Medication compliance		
Concomitant Medication		
Diary Card Review ⁷		
Adverse Experiences ⁸		
COPD Exacerbation assessment/Healthcare Ut.		
Physical (Including Respiratory) Examination		
Resting 12-Lead ECG		
Vital Signs (BP, HR) ³		
Overall Breathlessness (Modified Borg)		
Exercise Tolerance Test - 6 Minute Walk		
Post Exercise Breathlessness		
Pulmonary Function Tests ⁴		
Laboratory Tests ⁵		
Pregnancy Test ⁶		
Quality of Life Assessment: SGRQ		
Quality of Life Assessment: SF-36		
Dispense Open-Label Medication		
Study Continuation / Withdrawal		

³ ***Orthostatic blood pressure and heart rate are measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal.***

⁴ ***To include FEV₁, FEV₆, FVC, FEF₂₅₋₇₅, FEF₇₅, and PEFR.***

⁵ ***Faecal occult blood is measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal. Baseline measure is taken from last FOB in Study 042 or Study 091***

⁶ ***Serum pregnancy test for female patients of child bearing potential. Urine test only is done at Follow-Up Visit.***

⁷ ***A Diary Card is issued at each visit. The patient will use the Diary Card to record if they feel different since the previous visit.***

⁸ ***Patients will be assessed for GI AEs at every visit.***

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Protocol	Centre Number	Patient Number	Patient Initials		
207499/040		0 0 0 0 0			

MODULE 34*Please do not split modules*

Module 34 : Visit 25 (Week 88) and Visit 26 (Week 92), Adverse Experiences, Conmeds, Medical Procedures, COPD Exacerbations, Resource Utilisation, Continuation/Withdrawal

CRF Pages 513 - 552

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

None

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Page	513

Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 	Visit Date			Visit 25 Week 88
				Day	Month	Year	

PRESENTATION TO CLINIC

Record time of presentation to clinic

24hr:min

Note: *Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.*

Record the date and time of the patient's last dose of short-acting beta₂ agonist
Day Month Yr
24hr:min
Record the date and time of the patient's last dose of long-acting beta₂ agonist
Day Month Yr
24hr:min

Record the date and time of the patient's last dose of anticholinergic

Day Month Yr
24hr:min

Has the patient smoked within the past 2 hours?

☐ No☐ Yes → If 'Yes' please record time
24hr:min
COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	 Day Month Yr	 Day Month Yr	 Day Month Yr	 Day Month Yr
Level of exacerbation (maximum intensity)	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.

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Page	514

Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						Visit 25 Week 88

RESOURCE UTILISATION FOR COPD EXACERBATIONS

If the patient has received any COPD exacerbation related medical care since the previous visit, please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

*Review the diary card for illegible/incomplete entries **in the presence of the patient***

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD Exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 25 Week 88

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	

Date and time of last dose of study medication prior to the study visit

[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70	[][]	[][]	[][]	[][]	[][][]

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤ 120%?

☐ No →

If 'No' please check the % compliance at the previous visit. If compliance was not ≥ 80% and ≤ 120% at the last visit, please withdraw the patient. Please complete the assessments for Visit 25 and the assessments for patients withdrawing or stopping the study at Visit 25, contained at the end of this visit.

☐ Yes

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Page	516

Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 25 Week 88

SMOKING STATUS

Does the patient currently smoke?

☐ No☐ Yes → If 'Yes' please record the average number of cigarettes per day : [][]**PULMONARY REHABILITATION PROGRAMME**

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit?

☐ No☐ Yes**LABORATORY TESTS**

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential). Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date

[][]	[][]	[][]
Day	Month	Yr

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below

Attach label here

Are there any **clinically significant worsenings** since the previous visit?☐ No☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module

Place the Quest laboratory report in the plastic wallet at the back of this module

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Page	517

Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 25 Week 88

URINALYSIS

Please perform urinalysis using the dipstick provided by Quest and record the results in the patient notes.

Urine Sample Date [][][][][][]
Day Month Yr

Are the dipstick results negative?

- ☐ No → If 'No' please send the sample to Quest for microscopy
☐ Yes

Are there any **clinically significant worsenings** since the previous visit on the Quest report?

- ☐ No
☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

PREGNANCY TEST

Is the patient a female of child-bearing potential?

- ☐ No
☐ Yes → If 'Yes' please request a pregnancy test on the Quest requisition form.

Is the patient pregnant?

- ☐ No
☐ Yes → If 'Yes' please withdraw the patient from the study, enter details in the Adverse Experience section. Complete the Early Withdrawal Visit (found in a separate book).

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Protocol		Patient Number	Patient Initials		Visit 25 Week 88
207499/040		0 0 0 0 0			

OVERALL BREATHLESSNESS ASSESSMENT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 25 Week 88

INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed: [][][] [][][] [][][]
Day Month Yr

Were any clinically significant changes noted since the last visit?

☐ No

☐ Yes → ☐ Improvement

☐ Worsening →

Enter details in the Adverse Experience section at the back of this module.

Place the ECG trace in the plastic wallet at the back of this module.

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Page	520

Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 25 Week 88

PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and/or anticholinergic medications and/or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

STUDY MEDICATION LABEL

Issue the patient one bottle of open-label study medication (70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

Attach study medication
label here

Give the patient the first dose of study medication with food and record the date and time of administration below.

Date and time of administration

[][]	[][]	[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:	min	

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Page	521

Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 25 Week 88

INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐ No →

If 'No' please complete the assessments for Visit 25 and the Assessments for Patients Withdrawing or Stopping the Study at Visit 25 contained on the following pages. Complete and fax the Withdrawal Form contained in the Withdrawal and Follow-Up Book.

☐ Yes →

If 'Yes' please:

- *Issue a new diary card. Remind the patient to record if they feel differently since starting the study*
- *Ask the patient to return for the next visit in 28 + / - 6 days.*
- **Remind the patient:**
 - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*
 - ii **not** *to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*
 - iii *to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonists (long-acting) for **12 hours** before the next visit.*
 - iv *to refrain from smoking for **2 hours** immediately preceding the visit.*
 - v *to bring back at the next visit any remaining study medication or study medication containers and the diary card.*
 - vi *to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.*

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Page	522

Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 25 Week 88

ASSESSMENTS FOR PATIENTS WITHDRAWING OR STOPPING THE STUDY

Complete the assessments below only for patients who are withdrawing early from the study or stopping the study because the product has been registered or because the sponsor has terminated the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a clinically significant worsening in the patient's physical condition since the previous examination?

☐ No

☐ Yes →

If 'Yes' record details in the Adverse Experience section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 25 Week 88

FAECAL OCCULT BLOOD TEST

Issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-Up Visit.

VITAL SIGNS - ORTHOSTATIC CHANGE**1st Measurement: After 5 Minutes Supine**

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the previous assessment?

☐ No

☐ Yes → If 'Yes' record details in the Adverse Experience section at the back of this module.

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Follow-Up Visit in 7 +/- 3 days.

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Protocol 207499/040	Centre Number	Patient Number	Patient Initials	Visit Date			Visit 26 Week 92
				Day	Month	Year	
		0 0 0 0 0					

PRESENTATION TO CLINIC

Record time of presentation to clinic

24hr:min		

Note: Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.

Record the date and time of the patient's last dose of short-acting beta₂ agonist

Day	Month	Yr	24hr:min		

Record the date and time of the patient's last dose of long-acting beta₂ agonist

Day	Month	Yr	24hr:min		

Record the date and time of the patient's last dose of anticholinergic

Day	Month	Yr	24hr:min		

Has the patient smoked within the past 2 hours?

☐ No☐ Yes → If 'Yes' please record time

24hr:min		

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	<table border="1"> <tr> <td></td> <td></td> <td></td> </tr> <tr> <td>Day</td> <td>Month</td> <td>Yr</td> </tr> </table>				Day	Month	Yr	<table border="1"> <tr> <td></td> <td></td> <td></td> </tr> <tr> <td>Day</td> <td>Month</td> <td>Yr</td> </tr> </table>				Day	Month	Yr	<table border="1"> <tr> <td></td> <td></td> <td></td> </tr> <tr> <td>Day</td> <td>Month</td> <td>Yr</td> </tr> </table>				Day	Month	Yr	<table border="1"> <tr> <td></td> <td></td> <td></td> </tr> <tr> <td>Day</td> <td>Month</td> <td>Yr</td> </tr> </table>				Day	Month	Yr
Day	Month	Yr																										
Day	Month	Yr																										
Day	Month	Yr																										
Day	Month	Yr																										
Level of exacerbation (maximum intensity)	☐ Level 1	☐ Level 1	☐ Level 1	☐ Level 1																								
	☐ Level 2	☐ Level 2	☐ Level 2	☐ Level 2																								
	☐ Level 3	☐ Level 3	☐ Level 3	☐ Level 3																								

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.

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Page	525

Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						Visit 26 Week 92

RESOURCE UTILISATION FOR COPD EXACERBATIONS

If the patient has received any COPD exacerbation related medical care since the previous visit, please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

*Review the diary card for illegible/incomplete entries **in the presence of the patient***

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD Exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.

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Page	526

Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 26 Week 92

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	

Date and time of last dose of study medication prior to the study visit

[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70	[][]	[][]	[][]	[][]	[][][]

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤ 120%?

☐ No →

If 'No' please check the % compliance at the previous visit. If compliance was not ≥ 80% and ≤ 120% at the last visit, please withdraw the patient. Please complete the assessments for Visit 26 and the assessments for patients withdrawing or stopping the study at Visit 26, contained at the end of this visit.

☐ Yes

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SMOKING STATUS

Does the patient currently smoke?

☐ No☐ Yes → If 'Yes' please record the average number of cigarettes per day : [][]**PULMONARY REHABILITATION PROGRAMME**

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit?

☐ No☐ Yes**LABORATORY TESTS***Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential). Please refer to the instructions on the Quest shipping form and manual.*

Blood Sample Date

[][]	[][]	[][]
Day	Month	Yr

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below

Attach label here

Are there any **clinically significant worsenings** since the previous visit?☐ No☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module**Place the Quest laboratory report in the plastic wallet at the back of this module*

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URINALYSIS

Please perform urinalysis using the dipstick provided by Quest and record the results in the patient notes.

Urine Sample Date

[][]	[][]	[][]
Day	Month	Yr

Are the dipstick results negative?

☐

No →

If 'No' please send the sample to Quest for microscopy☐

Yes

Are there any **clinically significant worsenings** since the previous visit on the Quest report?☐

No

☐

Yes →

*If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.***PREGNANCY TEST**

Is the patient a female of child-bearing potential?

☐

No

☐

Yes →

If 'Yes' please request a pregnancy test on the Quest requisition form.

Is the patient pregnant?

☐

No

☐

Yes →

If 'Yes' please withdraw the patient from the study, enter details in the Adverse Experience section. Complete the Early Withdrawal Visit (found in a separate book).

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OVERALL BREATHLESSNESS ASSESSMENT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed: [][][] [][][] [][][]
Day Month Yr

Were any clinically significant changes noted since the last visit?

☐ No

☐ Yes → ☐ Improvement

☐ Worsening →

Enter details in the Adverse Experience section at the back of this module.

Place the ECG trace in the plastic wallet at the back of this module.

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PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and/or anticholinergic medications and/or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

STUDY MEDICATION LABEL

Issue the patient one bottle of open-label study medication (70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

Attach study medication
label here

Give the patient the first dose of study medication with food and record the date and time of administration below.

Date and time of administration [][] [][] [][] [][] [][]
Day Month Yr 24hr:min

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INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐ No →

If 'No' please complete the assessments for Visit 26 and the Assessments for Patients Withdrawing or Stopping the Study at Visit 26 contained on the following pages. Complete and fax the Withdrawal Form contained in the Withdrawal and Follow-Up Book.

☐ Yes →

If 'Yes' please:

- *Issue a new diary card. Remind the patient to record if they feel differently since starting the study*
- *Ask the patient to return for the next visit in 28 + / - 6 days.*
- **Remind the patient:**
 - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*
 - ii **not** *to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*
 - iii *to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonists (long-acting) for **12 hours** before the next visit.*
 - iv *to refrain from smoking for **2 hours** immediately preceding the visit.*
 - v *to bring back at the next visit any remaining study medication or study medication containers and the diary card.*
 - vi *to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.*

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ASSESSMENTS FOR PATIENTS WITHDRAWING OR STOPPING THE STUDY

Complete the assessments below only for patients who are withdrawing early from the study or stopping the study because the product has been registered or because the sponsor has terminated the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a clinically significant worsening in the patient's physical condition since the previous examination?

☐ No

☐ Yes →

If 'Yes' record details in the Adverse Experience section at the back of this module.

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FAECAL OCCULT BLOOD TEST

Issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-Up Visit.

VITAL SIGNS - ORTHOSTATIC CHANGE**1st Measurement: After 5 Minutes Supine**

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the previous assessment?

☐ No

☐ Yes → If 'Yes' record details in the Adverse Experience section at the back of this module.

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Follow-Up Visit in 7 +/- 3 days.

ADVERSE EXPERIENCES (Non-serious)**DEFINITIONS****INTENSITY (Maximum)**

<i>MILD</i>	<i>Adverse experience which is easily tolerated</i>
<i>MODERATE</i>	<i>Adverse experience sufficiently discomforting to interfere with daily activities</i>
<i>SEVERE</i>	<i>Adverse experience which prevents normal everyday activities</i>

RELATIONSHIP TO INVESTIGATIONAL DRUG

<i>NOT RELATED</i>	<i>The adverse experience is definitely not related to the test drug</i>
<i>UNLIKELY</i>	<i>There are other more likely causes and the drug is not suspected as a cause</i>
<i>SUSPECTED (REASONABLE POSSIBILITY)</i>	<i>A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug</i>
<i>PROBABLE</i>	<i>There probably is a direct cause and effect relationship between the adverse experience and the study drug</i>

SERIOUS ADVERSE EXPERIENCE (SAE)

An SAE is any event which is :-

- 1 - fatal
- 2 - life threatening
- 3 - disabling/incapacitating
- 4 - results in hospitalisation (excluding elective surgery or routine clinical procedures)
- 5 - prolongs a hospital stay
- 6 - associated with congenital abnormality
- 7 - cancer
- 8 - associated with overdose
- 9 - In addition any event which the investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug should be reported as a serious event

IF AN SAE OCCURS, PLEASE GO TO SAE SECTION IMMEDIATELY AND FOLLOW THE INSTRUCTIONS GIVEN THERE

Use each form for a maximum of two experiences

PLEASE REMEMBER ALL QUESTIONS ON ADVERSE EXPERIENCES FORM SHOULD BE COMPLETED

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ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous module?" Provide the diagnosis, **not** symptoms, where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbations section

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no adverse experiences occurred since the previous module, please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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ADVERSE EXPERIENCES (Non-serious)

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If no further adverse experiences or changes in adverse experiences occurred since the previous module, please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
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Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

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Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the previous module.
(Please write using BLOCK CAPITALS).

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

☐ No concomitant medication changes since the previous module

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experience section using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the new start and end date.

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)			
					Day	Mth	Yr	Day	Mth	Yr	
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* For Route, see tab for acceptable abbreviations.											

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CONCOMITANT MEDICATION - Continued

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experience section using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the new start and end date.

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)			
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MEDICAL PROCEDURES - (Excluding treatment for COPD Exacerbations)

Do not record procedures used to treat COPD exacerbations here, record them in the COPD Exacerbations section.

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed since the previous module?

☐ No

☐ Yes → *If 'Yes', please record details below using standard medical terminology (Please print clearly)*

All indications for procedures should be recorded in the Adverse Experience section

Procedure	Indication	Procedure Start Date			Procedure End Date																										
		Day	Mth	Yr	Day	Mth	Yr																								
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Protocol	Centre Number	Patient Number	Patient Initials		
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DETAILS OF COPD EXACERBATIONS

An exacerbation of COPD is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy. All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages**

If no COPD Exacerbations since the previous module please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome If patient died, STOP: go to the COPD SAE section and follow instructions given there	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____ Date : Day Month Yr		

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Page	542

Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

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If no further COPD exacerbations or changes to COPD exacerbations have occurred since the previous module please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
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End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
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Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____ Date : Day Month Yr		

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Page 543

Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

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Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)**SAEs MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS****COMPLETE THE SAE PAGES OPPOSITE**

Please complete these pages as fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Experience Course' blank and update it later

SIGN AND DATE THE SAE PAGE**PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE**

- Demography
- Significant Medical/Surgical History and Physical Examination
- Study Medication Record
- Concomitant Medication
- Form D (if applicable)

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE
(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO:

Your local SB CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local SB CRA/Medical monitor within 24 hours

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience <i>(Please print clearly)</i>	COPD Exacerbation	→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	 Day Month Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) <i>Please specify</i> _____ ☐ Another condition (eg, condition under study, intercurrent illness) <i>Please specify</i> _____ ☐ Another drug <i>Please specify</i> _____
Corrective Therapy <i>If 'Yes', record details in the COPD Medication or Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Page	545

Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 	SB Receipt Date			
				Day	Month	Year	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	 Day Month Yr			
	 Day Month Yr			
	 Day Month Yr			
	 Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

Day Month Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

Day Month Year

Please PRINT Name

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience <i>(Please print clearly)</i>	COPD Exacerbation	→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	 Day Month Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) <i>Please specify _____</i> ☐ Another condition (eg, condition under study, intercurrent illness) <i>Please specify _____</i> ☐ Another drug <i>Please specify _____</i>
Corrective Therapy <i>If 'Yes', record details in the COPD Medication or Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Page	547

Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]	SB Receipt Date Day Month Year [][][][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	Day Month Yr [][][][][]			
	Day Month Yr [][][][][]			
	Day Month Yr [][][][][]			
	Day Month Yr [][][][][]			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

[][][][][]

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

[][]	[][][]	[][]
Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

[][]	[][][]	[][]
Day	Month	Year

Please PRINT Name

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Page	548

Protocol 207499/040	Centre Number <table border="1"><tr><td></td><td></td><td></td></tr></table>				Patient Number <table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						
0	0	0	0	0													

MEDICATION FOR COPD EXACERBATIONSHas the patient taken any medication for **COPD exacerbations** since the previous module?☐ No☐ Yes → If 'Yes', please record details below

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)			
					Day	Mth	Yr	Day	Mth	Yr	
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											
* For Route, see tab for acceptable abbreviations.											

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Page	549

Protocol 207499/040	Centre Number [][][]	Patient Number 0 0 0 0 0	Patient Initials [][][][]		

MEDICAL PROCEDURES FOR COPD EXACERBATIONS

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since the previous module?

☐ No

☐ Yes → If 'Yes', please record details below using standard medical terminology

Procedure	Indication	Procedure Start Date			Procedure End Date		
		Day	Mth	Yr	Day	Mth	Yr
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							

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Protocol 207499/040	Centre Number <table border="1"><tr><td></td><td></td><td></td></tr></table>				Patient Number <table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						
0	0	0	0	0													

HEALTHCARE RESOURCE UTILISATION FOR COPD EXACERBATIONS

Complete this form for any **COPD exacerbation related medical care** the patient received since the previous module

Physician Visits (i.e., COPD care excluding scheduled protocol visits)

☐ There were no physician visits since the previous module

Date of Visit				Reason for Visit
Day	Mth	Yr		

Emergency Room (ER)/Urgent Care Visits/Casualty Department Procedures (i.e., lung surgery)

☐ There were no Emergency Room/Urgent Care Visits/Casualty Department Procedures since previous module

Date of Visit			Reason for Visit	Patient Admitted from ER?	
				Yes	No
Day	Mth	Yr		☐	☐
				☐	☐
				☐	☐
				☐	☐
				☐	☐
				☐	☐
				☐	☐

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Page	551

Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]		

HEALTHCARE RESOURCE UTILISATION FOR COPD EXACERBATIONS - (cont)

Hospitalisations (also record details of any hospitalisation in the Serious Adverse Experience - COPD Exacerbation section)

☐ There were no hospitalisations since the previous module

Date of Admission Day Mth Yr	Date of Discharge Day Mth Yr	Reason for Admission
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	

Intensive Care Unit (ICU) stays (did the patient stay in the ICU during any of the above hospitalisations?)

☐ There were no ICU stays since previous module

Date Admitted to ICU Day Mth Yr	Date Discharged from ICU Day Mth Yr	Reason for ICU Admission
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	

Lost Work Days (i.e., days patient missed work due to COPD excluding scheduled protocol visits)

☐ There were no lost work days since the previous module

Stop Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	

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Page	552

Protocol 207499/040	Centre Number <table border="1"><tr><td></td><td></td><td></td></tr></table>				Patient Number <table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						
0	0	0	0	0													

STUDY CONTINUATION/WITHDRAWAL

Is the patient continuing in the study?

☐ Yes☐ No →

*If 'No' please mark the **primary** cause of withdrawal and enter the date of the final visit and the date of the final dose*

[1] ☐ Adverse experience (complete AE or SAE section)[2] ☐ Insufficient therapeutic effect[3] ☐ Protocol deviation (including non-compliance)[4] ☐ Lost to follow-up[5] ☐ Other - specify: _____

Date of Final Visit

Day	Month	Yr	

Date of Final dose

Day	Month	Yr	

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data on this case report form and that all information is complete and accurate.

Investigator's Signature

Date

Day	Month	Yr	

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)

SAEs MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS

COMPLETE THE SAE PAGES OPPOSITE

Please complete these pages as fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Experience Course' blank and update it later

SIGN AND DATE THE SAE PAGE**PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE**

- Demography
- Significant Medical/Surgical History and Physical Examination
- Study Medication Record
- Medical Procedures
- Concomitant Medication
- Form D (if applicable)

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE

(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO:

Your local SB CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local SB CRA/Medical monitor within 24 hours

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Protocol	Centre Number	Patient Number	Patient Initials		
207499/040		0 0 0 0 0			

MOD35 & MOD36 - SERIOUS ADVERSE EXPERIENCES

MOD35 & MOD36	Serious Adverse Experiences
MOD29 :	553, 554
MOD30 :	555, 556



SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date		
				Day	Month	Year
207499/040		0 0 0 0 0				

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience <i>(Please print clearly)</i>		→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	 Day Month Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) Please specify _____ ☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____ ☐ Another drug Please specify _____
Corrective Therapy <i>If 'Yes', record details in the Concomitant Medication or Medical Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Protocol 207499/040	Centre Number <table border="1"><tr><td></td><td></td><td></td></tr></table>				Patient Number <table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>					SB Receipt Date Day Month Year <table border="1"><tr><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>							
0	0	0	0	0																			

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range								
	<table><tr><td></td><td></td><td></td><td></td></tr><tr><td>Day</td><td>Month</td><td>Yr</td><td></td></tr></table>					Day	Month	Yr				
Day	Month	Yr										
	<table><tr><td></td><td></td><td></td><td></td></tr><tr><td>Day</td><td>Month</td><td>Yr</td><td></td></tr></table>					Day	Month	Yr				
Day	Month	Yr										
	<table><tr><td></td><td></td><td></td><td></td></tr><tr><td>Day</td><td>Month</td><td>Yr</td><td></td></tr></table>					Day	Month	Yr				
Day	Month	Yr										
	<table><tr><td></td><td></td><td></td><td></td></tr><tr><td>Day</td><td>Month</td><td>Yr</td><td></td></tr></table>					Day	Month	Yr				
Day	Month	Yr										

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

Day	Month	Year

Please PRINT Name

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience <i>(Please print clearly)</i>		→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	 Day Month Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) Please specify _____ ☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____ ☐ Another drug Please specify _____
Corrective Therapy <i>If 'Yes', record details in the Concomitant Medication or Medical Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Page	556

Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]	SB Receipt Date Day Month Year [][][][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

[]	[]	[]	[]	[]

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

Day	Month	Year
[][]	[][]	[][]

Please PRINT Name

SB Medical Monitor's Signature:

Date

Day	Month	Year
[][]	[][]	[][]

Please PRINT Name

Protocol	Centre Number	Patient Number	Patient Initials
207499/040		0 0 0 0 0	

CONFIDENTIAL



PROTOCOL 207499/040

BOOK 13 : VISITS 27 AND 28 (WEEKS 96 AND 100)

**A MULTICENTRE, OPEN-LABEL EXTENSION STUDY TO EVALUATE
THE SAFETY, TOLERABILITY AND EFFICACY OF ORAL SB 207499
(15mg TWICE DAILY) IN PATIENTS WITH CHRONIC OBSTRUCTIVE
PULMONARY DISEASE (COPD)**

GENERAL INSTRUCTIONS

- Write clearly in capital letters using a black ball point pen and press firmly so that all copies are legible
- Do not write in shaded areas
- Answer ALL questions on every page
- Enter "N/A" if information requested is not available
- Initial and date all changes, additions or deletions. Use a single pen stroke to remove an incorrect entry
- Enter the patient initials on all pages on which information has been entered and the patient number and centre number where required
- Do not enter additional data/information after the set of CRF pages has been split/separated
- The cover flap or plastic writing board should be used to divide each set of pages before writing on them with a ball point pen

DATE

Please use the following three-letter abbreviations for the months

January	JAN
February	FEB
March	MAR
April	APR
May	MAY
June	JUN
July	JUL
August	AUG
September	SEP
October	OCT
November	NOV
December	DEC

e.g.

0	1	J	A	N	9	9
Day		Month			Year	

 = 1st January 1999

TIME

Unless specified otherwise, please use the 24 hour clock

e.g.

1	5	3	0
24hr:min			

 = 3.30 p.m

PATIENT INITIALS

Please use the following format:

e.g.

ROUTE KEY FOR PRIOR/CONCOMITANT MEDICATION PAGE

PO = By mouth	SL = Sublingual	TD = Transdermal
IV = Intravenous	IT = Intrathecal	IH = Inhaled
IM = Intramuscular	VA = Vaginal	SC = Subcutaneous
IAR = Intra-arterial	NA = Nasal	PR = Rectal
TO = Topical	IA = Intra-articular injection	ID = Intradermal

**SUMMARY CHART OF STUDY PROCEDURES (OPEN BOXES)
PROTOCOL SB 207499/040**

Mark open boxes to confirm that each procedure has been completed.

Procedures	Visit 27	Visit 28
	Week 96	Week 100
Signed written informed consent		
Study Medication compliance		
Concomitant Medication		
Diary Card Review ⁷		
Adverse Experiences ⁸		
COPD Exacerbation assessment/Healthcare Ut.		
Physical (Including Respiratory) Examination		
Resting 12-Lead ECG		
Vital Signs (BP, HR) ³		
Overall Breathlessness (Modified Borg)		
Exercise Tolerance Test - 6 Minute Walk		
Post Exercise Breathlessness		
Pulmonary Function Tests ⁴		
Laboratory Tests ⁵		
Pregnancy Test ⁶		
Quality of Life Assessment: SGRQ		
Quality of Life Assessment: SF-36		
Dispense or re-dispense Open-Label Medication		
Study Continuation / Withdrawal		

³ ***Orthostatic blood pressure and heart rate are measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal.***

⁴ ***To include FEV₁, FEV₆, FVC, FEF₂₅₋₇₅, FEF₇₅, and PEFR.***

⁵ ***Faecal occult blood is measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal. Baseline measure is taken from last FOB in Study 042 or Study 091***

⁶ ***Serum pregnancy test for female patients of child bearing potential. Urine test only is done at Follow-Up Visit.***

⁷ ***A Diary Card is issued at each visit. The patient will use the Diary Card to record if they feel different since the previous visit.***

⁸ ***Patients will be assessed for GI AEs at every visit.***

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Protocol	Centre Number	Patient Number	Patient Initials		
207499/040		0 0 0 0 0			

MODULE 37

Please do not split modules

Module 37 : Visit 27 (Week 96) and Visit 28 (Week 100), Adverse Experiences, Conmeds, Medical Procedures, COPD Exacerbations, Resource Utilisation, Continuation/Withdrawal

CRF Pages 557 - 599

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

Visit 27 :
SGRQ
SF36

00000



Page	557

Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]	Visit Date			Visit 27 Week 96
				Day [][]	Month [][]	Year [][]	

PRESENTATION TO CLINIC

Record time of presentation to clinic

[][]	[][]
24hr:min	

Note: *Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.*

Record the date and time of the patient's last dose of short-acting beta₂ agonist

[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:min

Record the date and time of the patient's last dose of long-acting beta₂ agonist

[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:min

Record the date and time of the patient's last dose of anticholinergic

[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:min

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes → If 'Yes' please record time

[][]	[][]
24hr:min	

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 27 Week 96

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of exacerbation (maximum intensity)	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						Visit 27 Week 96

RESOURCE UTILISATION FOR COPD EXACERBATIONS

If the patient has received any COPD exacerbation related medical care since the previous visit, please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

*Review the diary card for illegible/incomplete entries **in the presence of the patient***

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD Exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes →

If 'Yes' record details in the Adverse Experience section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 27 Week 96

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	

Date and time of last dose of study medication prior to the study visit

[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70	[][]	[][]	[][]	[][]	[][][]

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance $\geq 80\%$ and $\leq 120\%$?

☐ No →

If 'No' please check the % compliance at the previous visit. If compliance was not $\geq 80\%$ and $\leq 120\%$ at the last visit, please withdraw the patient. Please complete the assessments for Visit 27.

☐ Yes

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 27 Week 96

SMOKING STATUS

Does the patient currently smoke?

☐ No☐ Yes → If 'Yes' please record the average number of cigarettes per day : [][]**PULMONARY REHABILITATION PROGRAMME**

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit?

☐ No☐ Yes**LABORATORY TESTS**

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential). Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date

[][]	[][]	[][]
Day	Month	Yr

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below

Attach label here

Are there any **clinically significant worsenings** since the previous visit?☐ No☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module

Place the Quest laboratory report in the plastic wallet at the back of this module

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][][]		Visit 27 Week 96

URINALYSIS

Please perform urinalysis using the dipstick provided by Quest and record the results in the patient notes.

Urine Sample Date

[][]	[][]	[][]
Day	Month	Yr

Are the dipstick results negative?

☐

No →

If 'No' please send the sample to Quest for microscopy☐

Yes

Are there any **clinically significant worsenings** since the previous visit on the Quest report?☐

No

☐

Yes →

*If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.***PREGNANCY TEST**

Is the patient a female of child-bearing potential?

☐

No

☐

Yes →

If 'Yes' please request a pregnancy test on the Quest requisition form.

Is the patient pregnant?

☐

No

☐

Yes →

If 'Yes' please withdraw the patient from the study, enter details in the Adverse Experience section. Complete the Early Withdrawal Visit (found in a separate book).

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Protocol		Patient Number	Patient Initials		Visit 27 Week 96
207499/040		0 0 0 0 0			

OVERALL BREATHLESSNESS ASSESSMENT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 27 Week 96

INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed: [][][] [][][] [][][]
Day Month Yr

Were any clinically significant changes noted since the last visit?

☐ No

☐ Yes → ☐ Improvement

☐ Worsening →

Enter details in the Adverse Experience section at the back of this module.

Place the ECG trace in the plastic wallet at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 27 Week 96

VITAL SIGNS - ORTHOSTATIC CHANGE**1st Measurement: After 5 Minutes Supine**

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the previous assessment?☐ No☐ Yes →

If 'Yes' record details in the Adverse Experience section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 27 Week 96

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes. If the patient was too ill to attempt the test, please mark the 'Yes' box and enter 0 for distance walked.

☐ No

☐ Yes → If 'Yes', Distance walked [][][] Metres

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

POST-EXERCISE BREATHLESSNESS (Immediately after the patient completes the exercise tolerance)

Heart Rate [][][] beats/min

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

- 0 Nothing at all
- 1 Very, very slight (just noticeable)
- 2 Very slight
- 3 Moderate
- 4 Somewhat severe
- 5 Severe
- 6
- 7 Very severe
- 8
- 9 Very, very severe (almost maximal)
- 10 Maximal

Post-exercise breathlessness score [][][]

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise tolerance test (rest for at least 10 minutes) before performing the pulmonary function tests.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 27 Week 96

PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and/or anticholinergic medications and/or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

STUDY MEDICATION LABEL

Issue the patient one bottle of open-label study medication (70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

Attach study medication
label here

Give the patient the first dose of study medication with food and record the date and time of administration below.

Date and time of administration

[][]	[][]	[][]	[][]	[][]	[][]
Day	Month	Yr	24hr	:	min

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 27 Week 96

INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐ No →

If 'No' please complete the assessments for Visit 27 and issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-Up Visit. Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return in 7 +/- 3 days for a Follow-Up Visit.

☐ Yes →

If 'Yes' please:

- *Issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the next visit.*
- *Issue a new diary card. Remind the patient to record if they feel differently since starting the study*
- *Ask the patient to return for the next visit in 28 +/- 6 days.*
- **Remind the patient:**
 - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*
 - ii **not** *to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*
 - iii *to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonists (long-acting) for **12 hours** before the next visit.*
 - iv *to refrain from smoking for **2 hours** immediately preceding the visit.*
 - v *to bring back at the next visit any remaining study medication or study medication containers and the diary card.*
 - vi *to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.*

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Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 	Visit Date			Visit 28 Week 100
				Day 	Month 	Year 	

PRESENTATION TO CLINIC

Record time of presentation to clinic

24hr:min

Note: Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.

Record the date and time of the patient's last dose of short-acting beta₂ agonist

Day Month Yr 24hr:min
Record the date and time of the patient's last dose of long-acting beta₂ agonist

Day Month Yr 24hr:min

Record the date and time of the patient's last dose of anticholinergic

Day Month Yr 24hr:min

Has the patient smoked within the past 2 hours?

☐ No☐ Yes → If 'Yes' please record time

24hr:min
COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	 Day Month Yr	 Day Month Yr	 Day Month Yr	 Day Month Yr
Level of exacerbation (maximum intensity)	☐ Level 1	☐ Level 1	☐ Level 1	☐ Level 1
	☐ Level 2	☐ Level 2	☐ Level 2	☐ Level 2
	☐ Level 3	☐ Level 3	☐ Level 3	☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.

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Protocol		Patient Number	Patient Initials		Visit 28 Week 100
207499/040		0 0 0 0 0			

RESOURCE UTILISATION FOR COPD EXACERBATIONS

Please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

Review the diary card for illegible/incomplete entries **in the presence of the patient**

ADVERSE EXPERIENCES

Please complete the Adverse Experience section at the back of this module. If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

Please complete the Concomitant Medication section at the back of this module. If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD Exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 28 Week 100

FAECAL OCCULT BLOOD TEST

Record the results of the faecal occult blood tests performed between visits 27 and 28

Test	Date of Collection Day Mth Yr	Was the faecal occult blood test positive ?
1	[][][][][]	☐ No ☐ Yes
2	[][][][][]	☐ No ☐ Yes
3	[][][][][]	☐ No ☐ Yes

Are these findings clinically significant ?

☐ No

☐ Yes → If 'Yes' record details in the Adverse Experiences section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 28 Week 100

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	

Date and time of last dose of study medication prior to the study visit

[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70	[][]	[][]	[][]	[][]	[][][]

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance $\geq 80\%$ and $\leq 120\%$?

☐ No →

If 'No' please check the % compliance at the previous visit. If compliance was not $\geq 80\%$ and $\leq 120\%$ at the last visit, please withdraw the patient. Please complete the assessments for Visit 28 and the assessments for patients withdrawing or stopping the study at Visit 28, contained at the end of this visit.

☐ Yes

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 28 Week 100

SMOKING STATUS

Does the patient currently smoke?

☐ No☐ Yes → If 'Yes' please record the average number of cigarettes per day : [][]**PULMONARY REHABILITATION PROGRAMME**

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit?

☐ No☐ Yes**LABORATORY TESTS**

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential). Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date

[][]	[][]	[][]
Day	Month	Yr

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below

Attach label here

Are there any **clinically significant worsenings** since the previous visit?☐ No☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module

Place the Quest laboratory report in the plastic wallet at the back of this module

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 28 Week 100

URINALYSIS

Please perform urinalysis using the dipstick provided by Quest and record the results in the patient notes.

Urine Sample Date [][][][][][]
 Day Month Yr

Are the dipstick results negative?

- ☐ No → *If 'No' please send the sample to Quest for microscopy*
- ☐ Yes

Are there any **clinically significant worsenings** since the previous visit on the Quest report?

- ☐ No
- ☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

PREGNANCY TEST

Is the patient a female of child-bearing potential?

- ☐ No
- ☐ Yes → *If 'Yes' please request a pregnancy test on the Quest requisition form.*

Is the patient pregnant?

- ☐ No
- ☐ Yes → *If 'Yes' please withdraw the patient from the study, enter details in the Adverse Experience section. Complete the Early Withdrawal Visit (found in a separate book).*

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Protocol		Patient Number	Patient Initials		Visit 28 Week 100
207499/040		0 0 0 0 0			

OVERALL BREATHLESSNESS ASSESSMENT

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 28 Week 100

INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed: [][] [][] [][]
Day Month Yr

Were any clinically significant changes noted since the last visit?

☐ No

☐ Yes → ☐ Improvement

☐ Worsening →

Enter details in the Adverse Experience section at the back of this module.

Place the ECG trace in the plastic wallet at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 28 Week 100

PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and/or anticholinergic medications and/or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

STUDY MEDICATION LABEL

Issue the patient one bottle of open-label study medication (70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

**Attach study medication
label here**

Give the patient the first dose of study medication with food and record the date and time of administration below.

Date and time of administration

[][]	[][]	[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:min		

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][][]		Visit 28 Week 100

INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐ No →

If 'No' please complete the assessments for Visit 28 and the Assessments for Patients Withdrawing or Stopping the Study at Visit 28 contained on the following pages. Complete and fax the Withdrawal Form contained in the Withdrawal and Follow-Up Book.

☐ Yes →

If 'Yes' please:

- *Issue a new diary card. Remind the patient to record if they feel differently since starting the study*
- *Ask the patient to return for the next visit in 28 +/- 6 days.*
- *Complete the Study Continuation / Withdrawal page at the back of this module.*
- **Remind the patient:**
 - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*
 - ii **not** *to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*
 - iii *to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonists (long-acting) for **12 hours** before the next visit.*
 - iv *to refrain from smoking for **2 hours** immediately preceding the visit.*
 - v *to bring back at the next visit any remaining study medication or study medication containers and the diary card.*
 - vi *to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.*

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 28 Week 100

ASSESSMENTS FOR PATIENTS WITHDRAWING OR STOPPING THE STUDY

Complete the assessments below only for patients who are withdrawing early from the study or stopping the study because the product has been registered or because the sponsor has terminated the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a clinically significant worsening in the patient's physical condition since the previous examination?

☐ No

☐ Yes →

If 'Yes' record details in the Adverse Experience section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 28 Week 100

FAECAL OCCULT BLOOD TEST

Issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-Up Visit.

VITAL SIGNS - ORTHOSTATIC CHANGE**1st Measurement: After 5 Minutes Supine**

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the previous assessment?

☐ No

☐ Yes → If 'Yes' record details in the Adverse Experience section at the back of this module.

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Follow-Up Visit in 7 +/- 3 days.

ADVERSE EXPERIENCES (Non-serious)**DEFINITIONS****INTENSITY (Maximum)**

<i>MILD</i>	<i>Adverse experience which is easily tolerated</i>
<i>MODERATE</i>	<i>Adverse experience sufficiently discomforting to interfere with daily activities</i>
<i>SEVERE</i>	<i>Adverse experience which prevents normal everyday activities</i>

RELATIONSHIP TO INVESTIGATIONAL DRUG

<i>NOT RELATED</i>	<i>The adverse experience is definitely not related to the test drug</i>
<i>UNLIKELY</i>	<i>There are other more likely causes and the drug is not suspected as a cause</i>
<i>SUSPECTED (REASONABLE POSSIBILITY)</i>	<i>A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug</i>
<i>PROBABLE</i>	<i>There probably is a direct cause and effect relationship between the adverse experience and the study drug</i>

SERIOUS ADVERSE EXPERIENCE (SAE)

An SAE is any event which is :-

- 1 - fatal
- 2 - life threatening
- 3 - disabling/incapacitating
- 4 - results in hospitalisation (excluding elective surgery or routine clinical procedures)
- 5 - prolongs a hospital stay
- 6 - associated with congenital abnormality
- 7 - cancer
- 8 - associated with overdose
- 9 - In addition any event which the investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug should be reported as a serious event

IF AN SAE OCCURS, PLEASE GO TO SAE SECTION IMMEDIATELY AND FOLLOW THE INSTRUCTIONS GIVEN THERE

Use each form for a maximum of two experiences

PLEASE REMEMBER ALL QUESTIONS ON ADVERSE EXPERIENCES FORM SHOULD BE COMPLETED

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous module?" Provide the diagnosis, **not** symptoms, where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbations section

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no adverse experiences occurred since the previous module, please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

Investigator's Signature _____ Date :
Day Month Yr

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

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For SmithKline Beecham		
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End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
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Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

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Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the previous module.
(Please write using BLOCK CAPITALS).

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

☐ No concomitant medication changes since the previous module

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experience section using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the new start and end date.

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)			
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* For Route, see tab for acceptable abbreviations.											

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Protocol	Centre Number	Patient Number	Patient Initials		
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CONCOMITANT MEDICATION - Continued

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experience section using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the new start and end date.

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)			
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MEDICAL PROCEDURES - (Excluding treatment for COPD Exacerbations)

Do not record procedures used to treat COPD exacerbations here, record them in the COPD Exacerbations section.

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed since the previous module?

☐ No

☐ Yes → If 'Yes', please record details below using standard medical terminology (Please print clearly)

All indications for procedures should be recorded in the Adverse Experience section

Procedure	Indication	Procedure Start Date			Procedure End Date																										
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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.

All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages**

If no COPD Exacerbations since the previous module please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome If patient died, STOP: go to the COPD SAE section and follow instructions given there ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____ Date : Day Month Yr		

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.

All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages**

If no further COPD exacerbations or changes to COPD exacerbations have occurred since the previous module please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome If patient died, STOP: go to the COPD SAE section and follow instructions given there ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

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Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
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Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
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Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)**SAEs MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS****COMPLETE THE SAE PAGES OPPOSITE**

Please complete these pages as fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Experience Course' blank and update it later

SIGN AND DATE THE SAE PAGE**PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE**

- Demography
- Significant Medical/Surgical History and Physical Examination
- Study Medication Record
- Concomitant Medication
- Form D (if applicable)

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE
(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO:

Your local SB CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local SB CRA/Medical monitor within 24 hours

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience <i>(Please print clearly)</i>	COPD Exacerbation	→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	Day Month Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) <i>Please specify</i> _____ ☐ Another condition (eg, condition under study, intercurrent illness) <i>Please specify</i> _____ ☐ Another drug <i>Please specify</i> _____
Corrective Therapy <i>If 'Yes', record details in the COPD Medication or Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 	SB Receipt Date			
				Day	Month	Year	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	 Day Month Yr			
	 Day Month Yr			
	 Day Month Yr			
	 Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

Day Month Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

Please PRINT Name

Day Month Year

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience <i>(Please print clearly)</i>	COPD Exacerbation	→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	Day Month Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) <i>Please specify</i> _____ ☐ Another condition (eg, condition under study, intercurrent illness) <i>Please specify</i> _____ ☐ Another drug <i>Please specify</i> _____
Corrective Therapy <i>If 'Yes', record details in the COPD Medication or Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 	SB Receipt Date			
				Day	Month	Year	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	 Day Month Yr			
	 Day Month Yr			
	 Day Month Yr			
	 Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

Day Month Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

Please PRINT Name

Day Month Year

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MEDICATION FOR COPD EXACERBATIONSHas the patient taken any medication for **COPD exacerbations** since the previous module?☐ No☐ Yes → If 'Yes', please record details below

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)			
					Day	Mth	Yr	Day	Mth	Yr	
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
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				COPD EXACERBATION							☐
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* For Route, see tab for acceptable abbreviations.

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Protocol 207499/040	Centre Number <table border="1"><tr><td></td><td></td><td></td></tr></table>				Patient Number <table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						
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MEDICAL PROCEDURES FOR COPD EXACERBATIONS

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since the previous module?

☐ No

☐ Yes → If 'Yes', please record details below using standard medical terminology

Procedure	Indication	Procedure Start Date			Procedure End Date																										
		Day	Mth	Yr	Day	Mth	Yr																								
	COPD EXACERBATION	<table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>						<table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>						<table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>						<table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>						<table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>					
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HEALTHCARE RESOURCE UTILISATION FOR COPD EXACERBATIONS

Complete this form for any **COPD exacerbation related medical care** the patient received since the previous module

Physician Visits (i.e., COPD care excluding scheduled protocol visits)

☐ There were no physician visits since the previous module

Date of Visit				Reason for Visit				
Day	Mth	Yr						
<table><tr><td></td><td></td><td></td><td></td></tr></table>								
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Emergency Room (ER)/Urgent Care Visits/Casualty Department Procedures (i.e., lung surgery)

☐ There were no Emergency Room/Urgent Care Visits/Casualty Department Procedures since previous module

Date of Visit			Reason for Visit	Patient Admitted from ER?															
				Yes	No														
Day	Mth	Yr																	
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HEALTHCARE RESOURCE UTILISATION FOR COPD EXACERBATIONS - (cont)

Hospitalisations (also record details of any hospitalisation in the Serious Adverse Experience - COPD Exacerbation section)

☐ There were no hospitalisations since the previous module

Date of Admission Day Mth Yr	Date of Discharge Day Mth Yr	Reason for Admission										
<table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>						<table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>						
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Intensive Care Unit (ICU) stays (did the patient stay in the ICU during any of the above hospitalisations?)

☐ There were no ICU stays since previous module

Date Admitted to ICU Day Mth Yr	Date Discharged from ICU Day Mth Yr	Reason for ICU Admission										
<table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>						<table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>						
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Lost Work Days (i.e., days patient missed work due to COPD excluding scheduled protocol visits)

☐ There were no lost work days since the previous module

Stop Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence										
<table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>						<table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>						
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Protocol	Centre Number	Patient Number	Patient Initials		
207499/040		0 0 0 0 0			

STUDY CONTINUATION/WITHDRAWAL

Is the patient continuing in the study?

☐ Yes☐ No →

*If 'No' please mark the **primary** cause of withdrawal and enter the date of the final visit and the date of the final dose*

[1] ☐ Adverse experience (complete AE or SAE section)[2] ☐ Insufficient therapeutic effect[3] ☐ Protocol deviation (including non-compliance)[4] ☐ Lost to follow-up[5] ☐ Other - specify: _____

Date of Final Visit

Day	Month	Yr	

Date of Final dose

Day	Month	Yr	

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data on this case report form and that all information is complete and accurate.

Investigator's Signature

Date

Day	Month	Yr	

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)

SAEs MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS

COMPLETE THE SAE PAGES OPPOSITE

Please complete these pages as fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Experience Course' blank and update it later

SIGN AND DATE THE SAE PAGE**PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE**

- Demography
- Significant Medical/Surgical History and Physical Examination
- Study Medication Record
- Medical Procedures
- Concomitant Medication
- Form D (if applicable)

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE

(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO:

Your local SB CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local SB CRA/Medical monitor within 24 hours

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Protocol	Centre Number	Patient Number	Patient Initials		
207499/040		0 0 0 0 0			

MOD38 & MOD39 - SERIOUS ADVERSE EXPERIENCES

MOD38 & MOD39	Serious Adverse Experiences
MOD38 :	599, 600
MOD39 :	601, 602

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Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date		
207499/040				Day	Month	Year
		0 0 0 0 0				

SERIOUS ADVERSE EXPERIENCE (SAE)

Person Reporting SAE (Please print clearly) _____		AEGIS Number
Serious Adverse Experience (Please print clearly)		→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	
Outcome If patient died, please complete Form D	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) Please specify _____ ☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____ ☐ Another drug Please specify _____
Corrective Therapy If 'Yes', record details in the Concomitant Medication or Medical Procedures section	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Page 600

Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 	SB Receipt Date			
				Day 	Month 	Year 	

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	 Day Month Yr			
	 Day Month Yr			
	 Day Month Yr			
	 Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

Day	Month	Year

Please PRINT Name



SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date		
				Day	Month	Year
207499/040		0 0 0 0 0				

Person Reporting SAE (Please print clearly) _____		AEGIS Number
Serious Adverse Experience (Please print clearly)		→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	
End Date and Time (If ongoing please leave blank)	Day Month Yr 24hr:min	
Outcome If patient died, please complete Form D	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) Please specify _____ ☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____ ☐ Another drug Please specify _____
Corrective Therapy If 'Yes', record details in the Concomitant Medication or Medical Procedures section	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Page	602

Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]	SB Receipt Date Day Month Year [][][][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

[][][][][]

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

[][][][][][]
Day Month Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

[][][][][][]
Day Month Year

Please PRINT Name

Protocol	Centre Number	Patient Number	Patient Initials
207499/040		0 0 0 0 0	

CONFIDENTIAL



PROTOCOL 207499/040

BOOK 14 : VISITS 29 AND 30 (WEEKS 104 AND 108)

**A MULTICENTRE, OPEN-LABEL EXTENSION STUDY TO EVALUATE
THE SAFETY, TOLERABILITY AND EFFICACY OF ORAL SB 207499
(15mg TWICE DAILY) IN PATIENTS WITH CHRONIC OBSTRUCTIVE
PULMONARY DISEASE (COPD)**

GENERAL INSTRUCTIONS

- Write clearly in capital letters using a black ball point pen and press firmly so that all copies are legible
- Do not write in shaded areas
- Answer ALL questions on every page
- Enter "N/A" if information requested is not available
- Initial and date all changes, additions or deletions. Use a single pen stroke to remove an incorrect entry
- Enter the patient initials on all pages on which information has been entered and the patient number and centre number where required
- Do not enter additional data/information after the set of CRF pages has been split/separated
- The cover flap or plastic writing board should be used to divide each set of pages before writing on them with a ball point pen

DATE

Please use the following three-letter abbreviations for the months

January	JAN
February	FEB
March	MAR
April	APR
May	MAY
June	JUN
July	JUL
August	AUG
September	SEP
October	OCT
November	NOV
December	DEC

e.g.

0	1	J	A	N	0	1
Day		Month			Year	

 = 1st January 2001

TIME

Unless specified otherwise, please use the 24 hour clock

e.g.

1	5	3	0
24hr:min			

 = 3.30 p.m

PATIENT INITIALS

Please use the following format:

e.g.

ROUTE KEY FOR PRIOR/CONCOMITANT MEDICATION PAGE

PO = By mouth	SL = Sublingual	TD = Transdermal
IV = Intravenous	IT = Intrathecal	IH = Inhaled
IM = Intramuscular	VA = Vaginal	SC = Subcutaneous
IAR = Intra-arterial	NA = Nasal	PR = Rectal
TO = Topical	IA = Intra-articular injection	ID = Intradermal

**SUMMARY CHART OF STUDY PROCEDURES (OPEN BOXES)
PROTOCOL SB 207499/040***Mark open boxes to confirm that each procedure has been completed.*

Procedures	Visit 29 Week 104	Visit 30 Week 108
Signed written informed consent		
Study Medication compliance		
Concomitant Medication		
Diary Card Review ⁷		
Adverse Experiences ⁸		
COPD Exacerbation assessment/Healthcare Ut.		
Physical (Including Respiratory) Examination		
Resting 12-Lead ECG		
Vital Signs (BP, HR) ³		
Overall Breathlessness (Modified Borg)		
Exercise Tolerance Test - 6 Minute Walk		
Post Exercise Breathlessness		
Pulmonary Function Tests ⁴		
Laboratory Tests ⁵		
Pregnancy Test ⁶		
Quality of Life Assessment: SGRQ		
Quality of Life Assessment: SF-36		
Dispense Open-Label Medication		
Study Continuation / Withdrawal		

³ *Orthostatic blood pressure and heart rate are measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal.*

⁴ *To include FEV₁, FEV₆, FVC, FEF₂₅₋₇₅, FEF₇₅, and PEFR.*

⁵ *Faecal occult blood is measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal. Baseline measure is taken from last FOB in Study 042 or Study 091*

⁶ *Serum pregnancy test for female patients of child bearing potential. Urine test only is done at Follow-Up Visit.*

⁷ *A Diary Card is issued at each visit. The patient will use the Diary Card to record if they feel different since the previous visit.*

⁸ *Patients will be assessed for GI AEs at every visit.*

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Protocol	Centre Number	Patient Number	Patient Initials		
207499/040		0 0 0 0 0			

MODULE 40*Please do not split modules*

Module 40 : Visit 29 (Week 104) and Visit 30 (Week 108), Adverse Experiences, Conmeds, Medical Procedures, COPD Exacerbations, Resource Utilisation, Continuation/Withdrawal

CRF Pages 603 - 626

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

None

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Page 603

Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 	Visit Date			Visit 29 Week 104
				Day 	Month 	Year 	

PRESENTATION TO CLINIC

Record time of presentation to clinic

24hr:min

Note: Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.

Record the date and time of the patient's last dose of short-acting beta₂ agonist

Day Month Yr 24hr:min
Record the date and time of the patient's last dose of long-acting beta₂ agonist

Day Month Yr 24hr:min

Record the date and time of the patient's last dose of anticholinergic

Day Month Yr 24hr:min

Has the patient smoked within the past 2 hours?

☐ No☐ Yes → If 'Yes' please record time

24hr:min
COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	 Day Month Yr	 Day Month Yr	 Day Month Yr	 Day Month Yr
Level of exacerbation (maximum intensity)	☐ Level 1	☐ Level 1	☐ Level 1	☐ Level 1
	☐ Level 2	☐ Level 2	☐ Level 2	☐ Level 2
	☐ Level 3	☐ Level 3	☐ Level 3	☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.

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Protocol		Patient Number	Patient Initials		Visit 29 Week 104
207499/040		0 0 0 0 0			

RESOURCE UTILISATION FOR COPD EXACERBATIONS

If the patient has received any COPD exacerbation related medical care since the previous visit, please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

*Review the diary card for illegible/incomplete entries **in the presence of the patient***

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD Exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 29 Week 104

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	

Date and time of last dose of study medication prior to the study visit

[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70	[][]	[][]	[][]	[][]	[][][]

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance $\geq 80\%$ and $\leq 120\%$?

☐ No →

If 'No' please check the % compliance at the previous visit. If compliance was not $\geq 80\%$ and $\leq 120\%$ at the last visit, please withdraw the patient. Please complete the assessments for Visit 29 and the assessments for patients withdrawing or stopping the study at Visit 29, contained at the end of this visit.

☐ Yes

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 29 Week 104

SMOKING STATUS

Does the patient currently smoke?

☐ No☐ Yes → If 'Yes' please record the average number of cigarettes per day : [][]**PULMONARY REHABILITATION PROGRAMME**

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit?

☐ No☐ Yes**LABORATORY TESTS**

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential). Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date

[][]	[][]	[][]
Day	Month	Yr

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below

Attach label here

Are there any **clinically significant worsenings** since the previous visit?☐ No☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module

Place the Quest laboratory report in the plastic wallet at the back of this module

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][][]		Visit 29 Week 104

URINALYSIS

Please perform urinalysis using the dipstick provided by Quest and record the results in the patient notes.

Urine Sample Date

[][]	[][]	[][]
Day	Month	Yr

Are the dipstick results negative?

☐

No →

If 'No' please send the sample to Quest for microscopy

☐

Yes

Are there any **clinically significant worsenings** since the previous visit on the Quest report?☐

No

☐

Yes →

If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

PREGNANCY TEST

Is the patient a female of child-bearing potential?

☐

No

☐

Yes →

If 'Yes' please request a pregnancy test on the Quest requisition form.

Is the patient pregnant?

☐

No

☐

Yes →

If 'Yes' please withdraw the patient from the study, enter details in the Adverse Experience section. Complete the Early Withdrawal Visit (found in a separate book).

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Protocol		Patient Number	Patient Initials		Visit 29 Week 104									
207499/040		<table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	<table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						
0	0	0	0	0										

OVERALL BREATHLESSNESS ASSESSMENT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 29 Week 104

INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed: [][] [][] [][]
Day Month Yr

Were any clinically significant changes noted since the last visit?

☐ No

☐ Yes → ☐ Improvement

☐ Worsening →

Enter details in the Adverse Experience section at the back of this module.

Place the ECG trace in the plastic wallet at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 29 Week 104

PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and/or anticholinergic medications and/or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

STUDY MEDICATION LABEL

Issue the patient one bottle of open-label study medication (70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

Attach study medication
label here

Give the patient the first dose of study medication with food and record the date and time of administration below.

Date and time of administration

[][]	[][]	[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:	min	

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Protocol		Patient Number	Patient Initials		Visit 29 Week 104
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INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐ No →

If 'No' please complete the assessments for Visit 29 and the Assessments for Patients Withdrawing or Stopping the Study at Visit 29 contained on the following pages. Complete and fax the Withdrawal Form contained in the Withdrawal and Follow-Up Book.

☐ Yes →

If 'Yes' please:

- *Issue a new diary card. Remind the patient to record if they feel differently since starting the study*
- *Ask the patient to return for the next visit in 28 + / - 6 days.*
- **Remind the patient:**
 - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*
 - ii **not** *to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*
 - iii *to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonists (long-acting) for **12 hours** before the next visit.*
 - iv *to refrain from smoking for **2 hours** immediately preceding the visit.*
 - v *to bring back at the next visit any remaining study medication or study medication containers and the diary card.*
 - vi *to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.*

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 29 Week 104

ASSESSMENTS FOR PATIENTS WITHDRAWING OR STOPPING THE STUDY

Complete the assessments below only for patients who are withdrawing early from the study or stopping the study because the product has been registered or because the sponsor has terminated the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a clinically significant worsening in the patient's physical condition since the previous examination?

☐ No

☐ Yes →

If 'Yes' record details in the Adverse Experience section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 29 Week 104

FAECAL OCCULT BLOOD TEST

Issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-Up Visit.

VITAL SIGNS - ORTHOSTATIC CHANGE**1st Measurement: After 5 Minutes Supine**

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the previous assessment?

☐ No

☐ Yes → If 'Yes' record details in the Adverse Experience section at the back of this module.

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Follow-Up Visit in 7 +/- 3 days.

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Protocol	Centre Number	Patient Number	Patient Initials	Visit Date	Visit 30 Week 108
207499/040		0 0 0 0 0		Day Month Year	

PRESENTATION TO CLINIC

Record time of presentation to clinic

 24hr:min

Note: *Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.*

Record the date and time of the patient's last dose of short-acting beta₂ agonist

Day	Month	Yr	24hr:min		

Record the date and time of the patient's last dose of long-acting beta₂ agonist

Day	Month	Yr	24hr:min		

Record the date and time of the patient's last dose of anticholinergic

Day	Month	Yr	24hr:min		

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes → If 'Yes' please record time

 24hr:min

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 30 Week 108

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	[][][][][] Day Month Yr	[][][][][] Day Month Yr	[][][][][] Day Month Yr	[][][][][] Day Month Yr
Level of exacerbation (maximum intensity)	☐ Level 1	☐ Level 1	☐ Level 1	☐ Level 1
	☐ Level 2	☐ Level 2	☐ Level 2	☐ Level 2
	☐ Level 3	☐ Level 3	☐ Level 3	☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 30 Week 108

RESOURCE UTILISATION FOR COPD EXACERBATIONS

Please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

Review the diary card for illegible/incomplete entries **in the presence of the patient**

ADVERSE EXPERIENCES

Please complete the Adverse Experience section at the back of this module. If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

Please complete the Concomitant Medication section at the back of this module. If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD Exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 30 Week 108

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	

Date and time of last dose of study medication prior to the study visit

[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70	[][]	[][]	[][]	[][]	[][][]

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance $\geq 80\%$ and $\leq 120\%$?

☐ No →

If 'No' please check the % compliance at the previous visit. If compliance was not $\geq 80\%$ and $\leq 120\%$ at the last visit, please withdraw the patient. Please complete the assessments for Visit 30 and the assessments for patients withdrawing or stopping the study at Visit 30, contained at the end of this visit.

☐ Yes

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 30 Week 108

SMOKING STATUS

Does the patient currently smoke?

☐ No☐ Yes → If 'Yes' please record the average number of cigarettes per day : [][]**PULMONARY REHABILITATION PROGRAMME**

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit?

☐ No☐ Yes**LABORATORY TESTS**

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential). Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date

[][]	[][]	[][]
Day	Month	Yr

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below

Attach label here

Are there any **clinically significant worsenings** since the previous visit?☐ No☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module

Place the Quest laboratory report in the plastic wallet at the back of this module

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][][]		Visit 30 Week 108

URINALYSIS

Please perform urinalysis using the dipstick provided by Quest and record the results in the patient notes.

Urine Sample Date [][][][][][]
Day Month Yr

Are the dipstick results negative?

- ☐ No → If 'No' please send the sample to Quest for microscopy
- ☐ Yes

Are there any **clinically significant worsenings** since the previous visit on the Quest report?

- ☐ No
- ☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

PREGNANCY TEST

Is the patient a female of child-bearing potential?

- ☐ No
- ☐ Yes → If 'Yes' please request a pregnancy test on the Quest requisition form.

Is the patient pregnant?

- ☐ No
- ☐ Yes → If 'Yes' please withdraw the patient from the study, enter details in the Adverse Experience section. Complete the Early Withdrawal Visit (found in a separate book).

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OVERALL BREATHLESSNESS ASSESSMENT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 30 Week 108

INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed: [][] [][] [][]
Day Month Yr

Were any clinically significant changes noted since the last visit?

☐ No

☐ Yes → ☐ Improvement

☐ Worsening →

Enter details in the Adverse Experience section at the back of this module.

Place the ECG trace in the plastic wallet at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 30 Week 108

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes. If the patient was too ill to attempt the test, please mark the 'Yes' box and enter 0 for distance walked.

☐ No

☐ Yes → If 'Yes', Distance walked [][][] Metres

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

POST-EXERCISE BREATHLESSNESS (Immediately after the patient completes the exercise tolerance)

Heart Rate [][][] beats/min

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

- 0 Nothing at all
- 1 Very, very slight (just noticeable)
- 2 Very slight
- 3 Moderate
- 4 Somewhat severe
- 5 Severe
- 6
- 7 Very severe
- 8
- 9 Very, very severe (almost maximal)
- 10 Maximal

Post-exercise breathlessness score

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise tolerance test (rest for at least 10 minutes) before performing the pulmonary function tests.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 30 Week 108

PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and/or anticholinergic medications and/or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

STUDY MEDICATION LABEL

Issue the patient one bottle of open-label study medication (70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

**Attach study medication
label here**

Give the patient the first dose of study medication with food and record the date and time of administration below.

Date and time of administration

[][]	[][]	[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:min		

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 30 Week 108

INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐ No →

If 'No' please complete the assessments for Visit 30 and the Assessments for Patients Withdrawing or Stopping the Study at Visit 30 contained on the following pages. Complete and fax the Withdrawal Form contained in the Withdrawal and Follow-Up Book.

☐ Yes →

If 'Yes' please:

- *Issue a new diary card. Remind the patient to record if they feel differently since starting the study*
- *Ask the patient to return for the next visit in 28 +/- 6 days.*
- *Complete the Study Continuation / Withdrawal page at the back of this module.*
- **Remind the patient:**
 - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*
 - ii **not** *to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*
 - iii *to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonists (long-acting) for **12 hours** before the next visit.*
 - iv *to refrain from smoking for **2 hours** immediately preceding the visit.*
 - v *to bring back at the next visit any remaining study medication or study medication containers and the diary card.*
 - vi *to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.*

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 30 Week 108

ASSESSMENTS FOR PATIENTS WITHDRAWING OR STOPPING THE STUDY

Complete the assessments below only for patients who are withdrawing early from the study or stopping the study because the product has been registered or because the sponsor has terminated the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a clinically significant worsening in the patient's physical condition since the previous examination?

☐ No

☐ Yes →

If 'Yes' record details in the Adverse Experience section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 30 Week 108

FAECAL OCCULT BLOOD TEST

Issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-Up Visit.

VITAL SIGNS - ORTHOSTATIC CHANGE**1st Measurement: After 5 Minutes Supine**

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the previous assessment?

☐ No

☐ Yes → If 'Yes' record details in the Adverse Experience section at the back of this module.

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Follow-Up Visit in 7 +/- 3 days.

ADVERSE EXPERIENCES (Non-serious)**DEFINITIONS****INTENSITY (Maximum)**

<i>MILD</i>	<i>Adverse experience which is easily tolerated</i>
<i>MODERATE</i>	<i>Adverse experience sufficiently discomforting to interfere with daily activities</i>
<i>SEVERE</i>	<i>Adverse experience which prevents normal everyday activities</i>

RELATIONSHIP TO INVESTIGATIONAL DRUG

<i>NOT RELATED</i>	<i>The adverse experience is definitely not related to the test drug</i>
<i>UNLIKELY</i>	<i>There are other more likely causes and the drug is not suspected as a cause</i>
<i>SUSPECTED (REASONABLE POSSIBILITY)</i>	<i>A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug</i>
<i>PROBABLE</i>	<i>There probably is a direct cause and effect relationship between the adverse experience and the study drug</i>

SERIOUS ADVERSE EXPERIENCE (SAE)

An SAE is any event which is :-

- 1 - fatal
- 2 - life threatening
- 3 - disabling/incapacitating
- 4 - results in hospitalisation (excluding elective surgery or routine clinical procedures)
- 5 - prolongs a hospital stay
- 6 - associated with congenital abnormality
- 7 - cancer
- 8 - associated with overdose
- 9 - In addition any event which the investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug should be reported as a serious event

IF AN SAE OCCURS, PLEASE GO TO SAE SECTION IMMEDIATELY AND FOLLOW THE INSTRUCTIONS GIVEN THERE

Use each form for a maximum of two experiences

PLEASE REMEMBER ALL QUESTIONS ON ADVERSE EXPERIENCES FORM SHOULD BE COMPLETED

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous module?" Provide the diagnosis, **not** symptoms, where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbations section

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no adverse experiences occurred since the previous module, please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]		

ADVERSE EXPERIENCES (Non-serious)

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If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no further adverse experiences or changes in adverse experiences occurred since the previous module, please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	[][][] Day Month Yr [][] 24hr:min	[][][] Day Month Yr [][] 24hr:min
End Date and Time (If ongoing please leave blank)	[][][] Day Month Yr [][] 24hr:min	[][][] Day Month Yr [][] 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes [][] ☐ Constant	☐ Intermittent → No. of episodes [][] ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____ Date : [][][] Day Month Yr		

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

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For SmithKline Beecham		
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Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
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Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the previous module.
(Please write using BLOCK CAPITALS).

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

☐ No concomitant medication changes since the previous module

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experience section using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the new start and end date.

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)			
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* For Route, see tab for acceptable abbreviations.											

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Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

CONCOMITANT MEDICATION - Continued

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experience section using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the new start and end date.

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)			
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MEDICAL PROCEDURES - (Excluding treatment for COPD Exacerbations)

Do not record procedures used to treat COPD exacerbations here, record them in the COPD Exacerbations section.

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed since the previous module?

☐ No

☐ Yes → If 'Yes', please record details below using standard medical terminology (Please print clearly)

All indications for procedures should be recorded in the Adverse Experience section

Procedure	Indication	Procedure Start Date			Procedure End Date																										
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*An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy. All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

If no COPD Exacerbations since the previous module please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome If patient died, STOP: go to the COPD SAE section and follow instructions given there	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____ Date : Day Month Yr		

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.

All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages**

If no further COPD exacerbations or changes to COPD exacerbations have occurred since the previous module please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome If patient died, STOP: go to the COPD SAE section and follow instructions given there ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____ Date : Day Month Yr		

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Page	635

Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

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Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome If patient died, STOP: go to the COPD SAE section and follow instructions given there ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)**SAEs MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS****COMPLETE THE SAE PAGES OPPOSITE**

Please complete these pages as fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Experience Course' blank and update it later

SIGN AND DATE THE SAE PAGE**PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE**

- Demography
- Significant Medical/Surgical History and Physical Examination
- Study Medication Record
- Concomitant Medication
- Form D (if applicable)

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE
(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO:

Your local SB CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local SB CRA/Medical monitor within 24 hours

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Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date		
207499/040				Day	Month	Year
		0 0 0 0 0				

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

Person Reporting SAE (Please print clearly) _____		AEGIS Number
Serious Adverse Experience (Please print clearly)	COPD Exacerbation	→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	
Outcome If patient died, please complete Form D	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) Please specify _____ ☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____ ☐ Another drug Please specify _____
Corrective Therapy If 'Yes', record details in the COPD Medication or Procedures section	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 	SB Receipt Date			
				Day	Month	Year	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	 Day Month Yr			
	 Day Month Yr			
	 Day Month Yr			
	 Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

Day Month Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

Day Month Year

Please PRINT Name



SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date		
				Day	Month	Year
207499/040		0 0 0 0 0				

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience <i>(Please print clearly)</i>	COPD Exacerbation	→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	Day Month Yr : 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	Day Month Yr : 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (<i>maximum</i>)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) <i>Please specify</i> _____ ☐ Another condition (eg, condition under study, intercurrent illness) <i>Please specify</i> _____ ☐ Another drug <i>Please specify</i> _____
Corrective Therapy <i>If 'Yes', record details in the COPD Medication or Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]	SB Receipt Date Day Month Year [][][][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

[][][][][]

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

[][][]	[][][]	[][][]
Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

Please PRINT Name

[][][]	[][][]	[][][]
Day	Month	Year

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MEDICATION FOR COPD EXACERBATIONSHas the patient taken any medication for **COPD exacerbations** since the previous module?☐ No☐ Yes → If 'Yes', please record details below

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)			
					Day	Mth	Yr	Day	Mth	Yr	
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
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				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											

* For Route, see tab for acceptable abbreviations.

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Protocol 207499/040	Centre Number [][][]	Patient Number 0 0 0 0 0	Patient Initials [][][][]		

MEDICAL PROCEDURES FOR COPD EXACERBATIONS

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since the previous module?

☐ No

☐ Yes → If 'Yes', please record details below using standard medical terminology

Procedure	Indication	Procedure Start Date			Procedure End Date		
		Day	Mth	Yr	Day	Mth	Yr
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							

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Protocol 207499/040	Centre Number <table border="1"><tr><td></td><td></td><td></td></tr></table>				Patient Number <table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						
0	0	0	0	0													

HEALTHCARE RESOURCE UTILISATION FOR COPD EXACERBATIONS

Complete this form for any **COPD exacerbation related medical care** the patient received since the previous module

Physician Visits (i.e., COPD care excluding scheduled protocol visits)

☐ There were no physician visits since the previous module

Date of Visit				Reason for Visit
Day	Mth	Yr		

Emergency Room (ER)/Urgent Care Visits/Casualty Department Procedures (i.e., lung surgery)

☐ There were no Emergency Room/Urgent Care Visits/Casualty Department Procedures since previous module

Date of Visit			Reason for Visit	Patient Admitted from ER?					
				Yes	No				
Day	Mth	Yr							
<table><tr><td></td><td></td><td></td><td></td><td></td></tr></table>								☐	☐
<table><tr><td></td><td></td><td></td><td></td><td></td></tr></table>								☐	☐
<table><tr><td></td><td></td><td></td><td></td><td></td></tr></table>								☐	☐
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<table><tr><td></td><td></td><td></td><td></td><td></td></tr></table>								☐	☐
<table><tr><td></td><td></td><td></td><td></td><td></td></tr></table>								☐	☐
<table><tr><td></td><td></td><td></td><td></td><td></td></tr></table>								☐	☐

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Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

HEALTHCARE RESOURCE UTILISATION FOR COPD EXACERBATIONS - (cont)

Hospitalisations (also record details of any hospitalisation in the Serious Adverse Experience - COPD Exacerbation section)

☐ There were no hospitalisations since the previous module

Date of Admission Day Mth Yr	Date of Discharge Day Mth Yr	Reason for Admission

Intensive Care Unit (ICU) stays (did the patient stay in the ICU during any of the above hospitalisations?)

☐ There were no ICU stays since previous module

Date Admitted to ICU Day Mth Yr	Date Discharged from ICU Day Mth Yr	Reason for ICU Admission

Lost Work Days (i.e., days patient missed work due to COPD excluding scheduled protocol visits)

☐ There were no lost work days since the previous module

Stop Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence

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Protocol	Centre Number	Patient Number	Patient Initials		
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STUDY CONTINUATION/WITHDRAWAL

Is the patient continuing in the study?

☐ Yes☐ No →

*If 'No' please mark the **primary** cause of withdrawal and enter the date of the final visit and the date of the final dose*

[1] ☐ Adverse experience (complete AE or SAE section)[2] ☐ Insufficient therapeutic effect[3] ☐ Protocol deviation (including non-compliance)[4] ☐ Lost to follow-up[5] ☐ Other - specify: _____

Date of Final Visit

Day	Month	Yr

Date of Final dose

Day	Month	Yr

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data on this case report form and that all information is complete and accurate.

Investigator's Signature

Date

Day	Month	Yr

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)

SAEs MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS

COMPLETE THE SAE PAGES OPPOSITE

Please complete these pages as fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Experience Course' blank and update it later

SIGN AND DATE THE SAE PAGE**PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE**

- Demography
- Significant Medical/Surgical History and Physical Examination
- Study Medication Record
- Medical Procedures
- Concomitant Medication
- Form D (if applicable)

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE

(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO:

Your local SB CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local SB CRA/Medical monitor within 24 hours

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Protocol	Centre Number	Patient Number	Patient Initials		
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MOD41 & MOD42 - SERIOUS ADVERSE EXPERIENCES

MOD41 & MOD42	Serious Adverse Experiences
MOD41 :	645, 646
MOD42 :	647, 648

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience <i>(Please print clearly)</i>		→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	Day Month Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) <i>Please specify</i> _____ ☐ Another condition (eg, condition under study, intercurrent illness) <i>Please specify</i> _____ ☐ Another drug <i>Please specify</i> _____
Corrective Therapy <i>If 'Yes', record details in the Concomitant Medication or Medical Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 	SB Receipt Date			
				Day	Month	Year	

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	 Day Month Yr			
	 Day Month Yr			
	 Day Month Yr			
	 Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

Day Month Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

Day Month Year

Please PRINT Name



SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date		
				Day	Month	Year
207499/040		0 0 0 0 0				

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience <i>(Please print clearly)</i>		→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	Day Month Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity <i>(maximum)</i>	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) <i>Please specify _____</i> ☐ Another condition (eg, condition under study, intercurrent illness) <i>Please specify _____</i> ☐ Another drug <i>Please specify _____</i>
Corrective Therapy <i>If 'Yes', record details in the Concomitant Medication or Medical Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 	SB Receipt Date			
				Day 	Month 	Year 	

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	 Day Month Yr			
	 Day Month Yr			
	 Day Month Yr			
	 Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

Day	Month	Year

Please PRINT Name

Protocol	Centre Number	Patient Number	Patient Initials
207499/040		0 0 0 0 0	

CONFIDENTIAL



PROTOCOL 207499/040

BOOK 15 : VISITS 31 AND 32 (WEEKS 112 AND 116)

**A MULTICENTRE, OPEN-LABEL EXTENSION STUDY TO EVALUATE
THE SAFETY, TOLERABILITY AND EFFICACY OF ORAL SB 207499
(15mg TWICE DAILY) IN PATIENTS WITH CHRONIC OBSTRUCTIVE
PULMONARY DISEASE (COPD)**

GENERAL INSTRUCTIONS

- Write clearly in capital letters using a black ball point pen and press firmly so that all copies are legible
- Do not write in shaded areas
- Answer ALL questions on every page
- Enter "N/A" if information requested is not available
- Initial and date all changes, additions or deletions. Use a single pen stroke to remove an incorrect entry
- Enter the patient initials on all pages on which information has been entered and the patient number and centre number where required

Do not enter additional data/information after the set of CRF pages has been split/separated

The cover flap or plastic writing board should be used to divide each set of pages before writing on them with a ball point pen

DATE

Please use the following three-letter abbreviations for the months

January	JAN
February	FEB
March	MAR
April	APR
May	MAY
June	JUN
July	JUL
August	AUG
September	SEP
October	OCT
November	NOV
December	DEC

e.g.

0	1	J	A	N	9	9
Day		Month			Year	

 = 1st January 1999

TIME

Unless specified otherwise, please use the 24 hour clock

e.g.

1	5	3	0
24hr:min			

 = 3.30 p.m

PATIENT INITIALS

Please use the following format:

e.g.

ROUTE KEY FOR PRIOR/CONCOMITANT MEDICATION PAGE

PO = By mouth	SL = Sublingual	TD = Transdermal
IV = Intravenous	IT = Intrathecal	IH = Inhaled
IM = Intramuscular	VA = Vaginal	SC = Subcutaneous
IAR = Intra-arterial	NA = Nasal	PR = Rectal
TO = Topical	IA = Intra-articular injection	ID = Intradermal

**SUMMARY CHART OF STUDY PROCEDURES (OPEN BOXES)
PROTOCOL SB 207499/040**

Mark open boxes to confirm that each procedure has been completed.

Procedures	Visit 31 Week 112	Visit 32 Week 116
Signed written informed consent		
Study Medication compliance		
Concomitant Medication		
Diary Card Review ⁷		
Adverse Experiences ⁸		
COPD Exacerbation assessment/Healthcare Ut.		
Physical (Including Respiratory) Examination		
Resting 12-Lead ECG		
Vital Signs (BP, HR) ³		
Overall Breathlessness (Modified Borg)		
Exercise Tolerance Test - 6 Minute Walk		
Post Exercise Breathlessness		
Pulmonary Function Tests ⁴		
Laboratory Tests ⁵		
Pregnancy Test ⁶		
Quality of Life Assessment: SGRQ		
Quality of Life Assessment: SF-36		
Dispense or re-dispense Open-Label Medication		
Study Continuation / Withdrawal		

³ **Orthostatic blood pressure and heart rate are measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal.**

⁴ **To include FEV₁, FEV₆, FVC, FEF₂₅₋₇₅, FEF₇₅, and PEFR.**

⁵ **Faecal occult blood is measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal. Baseline measure is taken from last FOB in Study 042 or Study 091**

⁶ **Serum pregnancy test for female patients of child bearing potential. Urine test only is done at Follow-Up Visit.**

⁷ **A Diary Card is issued at each visit. The patient will use the Diary Card to record if they feel different since the previous visit.**

⁸ **Patients will be assessed for GI AEs at every visit.**

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Protocol	Centre Number	Patient Number	Patient Initials		
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MODULE 53

Please do not split modules

Module 53 : Visit 31 (Week 112) and Visit 32 (Week 116), Adverse Experiences, Conmeds, Medical Procedures, COPD Exacerbations, Resource Utilisation, Continuation/Withdrawal

CRF Pages 743 - 782

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

None

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 	Visit Date			Visit 31 Week 112
				Day 	Month 	Year 	

PRESENTATION TO CLINIC

Record time of presentation to clinic

24hr:min

Note: Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.

Record the date and time of the patient's last dose of short-acting beta₂ agonist

Day Month Yr 24hr:min
Record the date and time of the patient's last dose of long-acting beta₂ agonist

Day Month Yr 24hr:min

Record the date and time of the patient's last dose of anticholinergic

Day Month Yr 24hr:min

Has the patient smoked within the past 2 hours?

☐ No☐ Yes → If 'Yes' please record time

24hr:min
COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	 Day Month Yr	 Day Month Yr	 Day Month Yr	 Day Month Yr
Level of exacerbation (maximum intensity)	☐ Level 1	☐ Level 1	☐ Level 1	☐ Level 1
	☐ Level 2	☐ Level 2	☐ Level 2	☐ Level 2
	☐ Level 3	☐ Level 3	☐ Level 3	☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 31 Week 112

RESOURCE UTILISATION FOR COPD EXACERBATIONS

If the patient has received any COPD exacerbation related medical care since the previous visit, please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

*Review the diary card for illegible/incomplete entries **in the presence of the patient***

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD Exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 31 Week 112

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	

Date and time of last dose of study medication prior to the study visit

[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70	[][]	[][]	[][]	[][]	[][][]

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance $\geq 80\%$ and $\leq 120\%$?

☐ No →

If 'No' please check the % compliance at the previous visit. If compliance was not $\geq 80\%$ and $\leq 120\%$ at the last visit, please withdraw the patient. Please complete the assessments for Visit 31 and the assessments for patients withdrawing or stopping the study at Visit 31, contained at the end of this visit.

☐ Yes

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 31 Week 112

SMOKING STATUS

Does the patient currently smoke?

☐ No☐ Yes → If 'Yes' please record the average number of cigarettes per day : [][]**PULMONARY REHABILITATION PROGRAMME**

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit?

☐ No☐ Yes**LABORATORY TESTS**

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential). Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date

[][]	[][]	[][]
Day	Month	Yr

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below

Attach label here

Are there any **clinically significant worsenings** since the previous visit?☐ No☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module

Place the Quest laboratory report in the plastic wallet at the back of this module

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 31 Week 112

URINALYSIS

Please perform urinalysis using the dipstick provided by Quest and record the results in the patient notes.

Urine Sample Date

[][]	[][]	[][]
Day	Month	Yr

Are the dipstick results negative?

☐

No →

If 'No' please send the sample to Quest for microscopy☐

Yes

Are there any **clinically significant worsenings** since the previous visit on the Quest report?☐

No

☐

Yes →

*If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.***PREGNANCY TEST**

Is the patient a female of child-bearing potential?

☐

No

☐

Yes →

If 'Yes' please request a pregnancy test on the Quest requisition form.

Is the patient pregnant?

☐

No

☐

Yes →

If 'Yes' please withdraw the patient from the study, enter details in the Adverse Experience section. Complete the Early Withdrawal Visit (found in a separate book).

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Protocol		Patient Number	Patient Initials		Visit 31 Week 112
207499/040		0 0 0 0 0			

OVERALL BREATHLESSNESS ASSESSMENT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 31 Week 112

INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed: [][] [][] [][]
Day Month Yr

Were any clinically significant changes noted since the last visit?

☐ No

☐ Yes → ☐ Improvement

☐ Worsening →

Enter details in the Adverse Experience section at the back of this module.

Place the ECG trace in the plastic wallet at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 31 Week 112

PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and/or anticholinergic medications and/or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

STUDY MEDICATION LABEL

Issue the patient one bottle of open-label study medication (70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

Attach study medication
label here

Give the patient the first dose of study medication with food and record the date and time of administration below.

Date and time of administration

[][]	[][]	[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:	min	

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Page	751

Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 31 Week 112

INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐ No →

If 'No' please complete the assessments for Visit 31 and the Assessments for Patients Withdrawing or Stopping the Study at Visit 31 contained on the following pages. Complete and fax the Withdrawal Form contained in the Withdrawal and Follow-Up Book.

☐ Yes →

If 'Yes' please:

- *Issue a new diary card. Remind the patient to record if they feel differently since starting the study*
- *Ask the patient to return for the next visit in 28 + / - 6 days.*
- **Remind the patient:**
 - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*
 - ii **not** *to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*
 - iii *to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonists (long-acting) for **12 hours** before the next visit.*
 - iv *to refrain from smoking for **2 hours** immediately preceding the visit.*
 - v *to bring back at the next visit any remaining study medication or study medication containers and the diary card.*
 - vi *to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.*

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 31 Week 112

ASSESSMENTS FOR PATIENTS WITHDRAWING OR STOPPING THE STUDY

Complete the assessments below only for patients who are withdrawing early from the study or stopping the study because the product has been registered or because the sponsor has terminated the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes →

If 'Yes' record details in the Adverse Experience section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 31 Week 112

FAECAL OCCULT BLOOD TEST

Issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-Up Visit.

VITAL SIGNS - ORTHOSTATIC CHANGE**1st Measurement: After 5 Minutes Supine**

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

Are there any clinically significant worsenings since the previous assessment?

☐ No

☐ Yes → If 'Yes' record details in the Adverse Experience section at the back of this module.

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Follow-Up Visit in 7 +/- 3 days.

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 	Visit Date			Visit 32 Week 116
				Day 	Month 	Year 	

PRESENTATION TO CLINIC

Record time of presentation to clinic

24hr:min

Note: Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.

Record the date and time of the patient's last dose of short-acting beta₂ agonist

Day Month Yr 24hr:min
Record the date and time of the patient's last dose of long-acting beta₂ agonist

Day Month Yr 24hr:min

Record the date and time of the patient's last dose of anticholinergic

Day Month Yr 24hr:min

Has the patient smoked within the past 2 hours?

☐ No☐ Yes → If 'Yes' please record time

24hr:min
COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	 Day Month Yr	 Day Month Yr	 Day Month Yr	 Day Month Yr
Level of exacerbation (maximum intensity)	☐ Level 1	☐ Level 1	☐ Level 1	☐ Level 1
	☐ Level 2	☐ Level 2	☐ Level 2	☐ Level 2
	☐ Level 3	☐ Level 3	☐ Level 3	☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.

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RESOURCE UTILISATION FOR COPD EXACERBATIONS

If the patient has received any COPD exacerbation related medical care since the previous visit, please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

*Review the diary card for illegible/incomplete entries **in the presence of the patient***

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD Exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 32 Week 116

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	

Date and time of last dose of study medication prior to the study visit

[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70	[][]	[][]	[][]	[][]	[][][]

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance $\geq 80\%$ and $\leq 120\%$?

☐ No →

If 'No' please check the % compliance at the previous visit. If compliance was not $\geq 80\%$ and $\leq 120\%$ at the last visit, please withdraw the patient. Please complete the assessments for Visit 32 and the assessments for patients withdrawing or stopping the study at Visit 32, contained at the end of this visit.

☐ Yes

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 32 Week 116

SMOKING STATUS

Does the patient currently smoke?

☐ No☐ Yes → If 'Yes' please record the average number of cigarettes per day : [][]**PULMONARY REHABILITATION PROGRAMME**

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit?

☐ No☐ Yes**LABORATORY TESTS**

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential). Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date

[][]	[][]	[][]
Day	Month	Yr

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below

Attach label here

Are there any **clinically significant worsenings** since the previous visit?☐ No☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module

Place the Quest laboratory report in the plastic wallet at the back of this module

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URINALYSIS

Please perform urinalysis using the dipstick provided by Quest and record the results in the patient notes.

Urine Sample Date

Day	Month	Yr		

Are the dipstick results negative?

- ☐ No → If 'No' please send the sample to Quest for microscopy
- ☐ Yes

Are there any **clinically significant worsenings** since the previous visit on the Quest report?

- ☐ No
- ☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

PREGNANCY TEST

Is the patient a female of child-bearing potential?

- ☐ No
- ☐ Yes → If 'Yes' please request a pregnancy test on the Quest requisition form.

Is the patient pregnant?

- ☐ No
- ☐ Yes → If 'Yes' please withdraw the patient from the study, enter details in the Adverse Experience section. Complete the Early Withdrawal Visit (found in a separate book).

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OVERALL BREATHLESSNESS ASSESSMENT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 32 Week 116

INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed: [][] [][] [][]
Day Month Yr

Were any clinically significant changes noted since the last visit?

☐ No

☐ Yes → ☐ Improvement

☐ Worsening →

Enter details in the Adverse Experience section at the back of this module.

Place the ECG trace in the plastic wallet at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 32 Week 116

PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and/or anticholinergic medications and/or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

STUDY MEDICATION LABEL

Issue the patient one bottle of open-label study medication (70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

**Attach study medication
label here**

Give the patient the first dose of study medication with food and record the date and time of administration below.

Date and time of administration

[][]	[][]	[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:min		

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 32 Week 116

INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐ No →

If 'No' please complete the assessments for Visit 32 and the Assessments for Patients Withdrawing or Stopping the Study at Visit 32 contained on the following pages. Complete and fax the Withdrawal Form contained in the Withdrawal and Follow-Up Book.

☐ Yes →

If 'Yes' please:

- *Issue a new diary card. Remind the patient to record if they feel differently since starting the study*
- *Ask the patient to return for the next visit in 28 +/- 6 days.*
- *Complete the Study Continuation / Withdrawal page at the back of this module.*
- **Remind the patient:**
 - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*
 - ii **not** *to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*
 - iii *to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonists (long-acting) for **12 hours** before the next visit.*
 - iv *to refrain from smoking for **2 hours** immediately preceding the visit.*
 - v *to bring back at the next visit any remaining study medication or study medication containers and the diary card.*
 - vi *to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.*

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ASSESSMENTS FOR PATIENTS WITHDRAWING OR STOPPING THE STUDY

Complete the assessments below only for patients who are withdrawing early from the study or stopping the study because the product has been registered or because the sponsor has terminated the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a clinically significant worsening in the patient's physical condition since the previous examination?

☐ No

☐ Yes →

If 'Yes' record details in the Adverse Experience section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 32 Week 116

FAECAL OCCULT BLOOD TEST

Issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-Up Visit.

VITAL SIGNS - ORTHOSTATIC CHANGE**1st Measurement: After 5 Minutes Supine**

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the previous assessment?

☐ No

☐ Yes → If 'Yes' record details in the Adverse Experience section at the back of this module.

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Follow-Up Visit in 7 +/- 3 days.

ADVERSE EXPERIENCES (Non-serious)**DEFINITIONS****INTENSITY (Maximum)**

<i>MILD</i>	<i>Adverse experience which is easily tolerated</i>
<i>MODERATE</i>	<i>Adverse experience sufficiently discomforting to interfere with daily activities</i>
<i>SEVERE</i>	<i>Adverse experience which prevents normal everyday activities</i>

RELATIONSHIP TO INVESTIGATIONAL DRUG

<i>NOT RELATED</i>	<i>The adverse experience is definitely not related to the test drug</i>
<i>UNLIKELY</i>	<i>There are other more likely causes and the drug is not suspected as a cause</i>
<i>SUSPECTED (REASONABLE POSSIBILITY)</i>	<i>A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug</i>
<i>PROBABLE</i>	<i>There probably is a direct cause and effect relationship between the adverse experience and the study drug</i>

SERIOUS ADVERSE EXPERIENCE (SAE)

An SAE is any event which is :-

- 1 - fatal
- 2 - life threatening
- 3 - disabling/incapacitating
- 4 - results in hospitalisation (excluding elective surgery or routine clinical procedures)
- 5 - prolongs a hospital stay
- 6 - associated with congenital abnormality
- 7 - cancer
- 8 - associated with overdose
- 9 - In addition any event which the investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug should be reported as a serious event

IF AN SAE OCCURS, PLEASE GO TO SAE SECTION IMMEDIATELY AND FOLLOW THE INSTRUCTIONS GIVEN THERE

Use each form for a maximum of two experiences

PLEASE REMEMBER ALL QUESTIONS ON ADVERSE EXPERIENCES FORM SHOULD BE COMPLETED

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous module?" Provide the diagnosis, **not** symptoms, where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbations section

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no adverse experiences occurred since the previous module, please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous module?" Provide the diagnosis, **not** symptoms, where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbations section

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no further adverse experiences or changes in adverse experiences occurred since the previous module, please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous module?" Provide the diagnosis, **not** symptoms, where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbations section

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no further adverse experiences or changes in adverse experiences occurred since the previous module, please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the previous module.
(Please write using BLOCK CAPITALS).

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

☐ No concomitant medication changes since the previous module

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experience section using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the new start and end date.

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)		
					Day	Mth	Yr	Day	Mth	Yr
					[][][][]	[][][][]	[][][][]	[][][][]	[][][][]	☐
For SB										
					[][][][]	[][][][]	[][][][]	[][][][]	[][][][]	☐
For SB										
					[][][][]	[][][][]	[][][][]	[][][][]	[][][][]	☐
For SB										
					[][][][]	[][][][]	[][][][]	[][][][]	[][][][]	☐
For SB										
					[][][][]	[][][][]	[][][][]	[][][][]	[][][][]	☐
For SB										
					[][][][]	[][][][]	[][][][]	[][][][]	[][][][]	☐
For SB										
					[][][][]	[][][][]	[][][][]	[][][][]	[][][][]	☐
For SB										
* For Route, see tab for acceptable abbreviations.										

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CONCOMITANT MEDICATION - Continued

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experience section using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the new start and end date.

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)			
					Day	Mth	Yr	Day	Mth	Yr	
											☐
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* For Route, see tab for acceptable abbreviations.

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Protocol 207499/040	Centre Number <table border="1"><tr><td></td><td></td><td></td></tr></table>				Patient Number <table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						
0	0	0	0	0													

MEDICAL PROCEDURES - (Excluding treatment for COPD Exacerbations)

Do not record procedures used to treat COPD exacerbations here, record them in the COPD Exacerbations section.

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed since the previous module?

☐ No

☐ Yes → If 'Yes', please record details below using standard medical terminology (Please print clearly)

All indications for procedures should be recorded in the Adverse Experience section

Procedure	Indication	Procedure Start Date			Procedure End Date																										
		Day	Mth	Yr	Day	Mth	Yr																								
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SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number	Patient Initials		
207499/040		0 0 0 0			

*An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy. All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages***

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome If patient died, STOP: go to the COPD SAE section and follow instructions given there	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____ Date : Day Month Yr		

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Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.

All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages**

If no further COPD exacerbations or changes to COPD exacerbations have occurred since the previous module please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome If patient died, STOP: go to the COPD SAE section and follow instructions given there ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____ Date : Day Month Yr		

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.

All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages**

If no further COPD exacerbations or changes to COPD exacerbations have occurred since the previous module please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome If patient died, STOP: go to the COPD SAE section and follow instructions given there ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)**SAEs MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS****COMPLETE THE SAE PAGES OPPOSITE**

Please complete these pages as fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Experience Course' blank and update it later

SIGN AND DATE THE SAE PAGE**PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE**

- Demography
- Significant Medical/Surgical History and Physical Examination
- Study Medication Record
- Concomitant Medication
- Form D (if applicable)

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE
(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO:

Your local SB CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local SB CRA/Medical monitor within 24 hours



SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date		
				Day	Month	Year
207499/040		0 0 0 0 0				

Person Reporting SAE (Please print clearly) _____		AEGIS Number	
Serious Adverse Experience (Please print clearly)	COPD Exacerbation	→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution	
For SmithKline Beecham			
Onset Date and Time Day Month Yr 24hr:min			
End Date and Time (If ongoing please leave blank)	Day Month Yr 24hr:min		
Outcome If patient died, please complete Form D	☐ Resolved ☐ Ongoing ☐ Died		
Experience Course	☐ Intermittent → No. of episodes ☐ Constant		
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe		
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No	
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) Please specify _____	
Corrective Therapy If 'Yes', record details in the COPD Medication or Procedures section	☐ Yes ☐ No	☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	☐ Another drug Please specify _____	

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 	SB Receipt Date			
				Day	Month	Year	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	 Day Month Yr			
	 Day Month Yr			
	 Day Month Yr			
	 Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

Day Month Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

Day Month Year

Please PRINT Name



SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date		
				Day	Month	Year
207499/040		0 0 0 0 0				

Person Reporting SAE (Please print clearly) _____		AEGIS Number
Serious Adverse Experience (Please print clearly)	COPD Exacerbation	→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time Day Month Yr 24hr:min		
End Date and Time (If ongoing please leave blank)	Day Month Yr 24hr:min	
Outcome If patient died, please complete Form D	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) Please specify _____ ☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____ ☐ Another drug Please specify _____
Corrective Therapy If 'Yes', record details in the COPD Medication or Procedures section	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]	SB Receipt Date Day Month Year [][][][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	Day Month Yr [][][][][]			
	Day Month Yr [][][][][]			
	Day Month Yr [][][][][]			
	Day Month Yr [][][][][]			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

[]	[]	[]	[]	[]

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

[][]	[][][]	[][]
Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

[][]	[][][]	[][]
Day	Month	Year

Please PRINT Name

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Protocol 207499/040	Centre Number <table border="1"><tr><td></td><td></td><td></td></tr></table>				Patient Number <table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						
0	0	0	0	0													

MEDICATION FOR COPD EXACERBATIONSHas the patient taken any medication for **COPD exacerbations** since the previous module?☐ No☐ Yes → If 'Yes', please record details below

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)			
					Day	Mth	Yr	Day	Mth	Yr	
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
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				COPD EXACERBATION							☐
For SB											
				COPD EXACERBATION							☐
For SB											
* For Route, see tab for acceptable abbreviations.											

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Protocol 207499/040	Centre Number [][][]	Patient Number 0 0 0 0 0	Patient Initials [][][][]		

MEDICAL PROCEDURES FOR COPD EXACERBATIONS

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since the previous module?

☐ No

☐ Yes → If 'Yes', please record details below using standard medical terminology

Procedure	Indication	Procedure Start Date			Procedure End Date		
		Day	Mth	Yr	Day	Mth	Yr
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							

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Protocol 207499/040	Centre Number <table border="1"><tr><td></td><td></td><td></td></tr></table>				Patient Number <table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						
0	0	0	0	0													

HEALTHCARE RESOURCE UTILISATION FOR COPD EXACERBATIONS

Complete this form for any **COPD exacerbation related medical care** the patient received since the previous module

Physician Visits (i.e., COPD care excluding scheduled protocol visits)

☐ There were no physician visits since the previous module

Date of Visit				Reason for Visit
Day	Mth	Yr		

Emergency Room (ER)/Urgent Care Visits/Casualty Department Procedures (i.e., lung surgery)

☐ There were no Emergency Room/Urgent Care Visits/Casualty Department Procedures since previous module

Date of Visit			Reason for Visit	Patient Admitted from ER?						
				Yes	No					
Day	Mth	Yr								
<table><tr><td></td><td></td><td></td><td></td><td></td></tr></table>									☐	☐
<table><tr><td></td><td></td><td></td><td></td><td></td></tr></table>									☐	☐
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Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]		

HEALTHCARE RESOURCE UTILISATION FOR COPD EXACERBATIONS - (cont)

Hospitalisations (also record details of any hospitalisation in the Serious Adverse Experience - COPD Exacerbation section)

☐ There were no hospitalisations since the previous module

Date of Admission Day Mth Yr	Date of Discharge Day Mth Yr	Reason for Admission
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	

Intensive Care Unit (ICU) stays (did the patient stay in the ICU during any of the above hospitalisations?)

☐ There were no ICU stays since previous module

Date Admitted to ICU Day Mth Yr	Date Discharged from ICU Day Mth Yr	Reason for ICU Admission
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	

Lost Work Days (i.e., days patient missed work due to COPD excluding scheduled protocol visits)

☐ There were no lost work days since the previous module

Stop Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

STUDY CONTINUATION/WITHDRAWAL

Is the patient continuing in the study?

☐ Yes☐ No →

*If 'No' please mark the **primary** cause of withdrawal and enter the date of the final visit and the date of the final dose*

[1] ☐ Adverse experience (complete AE or SAE section)[2] ☐ Insufficient therapeutic effect[3] ☐ Protocol deviation (including non-compliance)[4] ☐ Lost to follow-up[5] ☐ Other - specify: _____

Date of Final Visit

Day	Month	Yr

Date of Final dose

Day	Month	Yr

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data on this case report form and that all information is complete and accurate.

Investigator's Signature _____

 Date

Day	Month	Yr

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)

SAEs MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS

COMPLETE THE SAE PAGES OPPOSITE

Please complete these pages as fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Experience Course' blank and update it later

SIGN AND DATE THE SAE PAGE**PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE**

- Demography
- Significant Medical/Surgical History and Physical Examination
- Study Medication Record
- Medical Procedures
- Concomitant Medication
- Form D (if applicable)

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE

(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO:

Your local SB CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local SB CRA/Medical monitor within 24 hours

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Protocol	Centre Number	Patient Number	Patient Initials		
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MOD54 & MOD55 - SERIOUS ADVERSE EXPERIENCES

MOD54 & MOD55	Serious Adverse Experiences
MOD54 :	783, 784
MOD55 :	785, 786



Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date		
				Day	Month	Year
207499/040		0 0 0 0 0				

SERIOUS ADVERSE EXPERIENCE (SAE)

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience <i>(Please print clearly)</i>		→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	Day Month Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) <i>Please specify</i> _____ ☐ Another condition (eg, condition under study, intercurrent illness) <i>Please specify</i> _____ ☐ Another drug <i>Please specify</i> _____
Corrective Therapy <i>If 'Yes', record details in the Concomitant Medication or Medical Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]	SB Receipt Date Day Month Year [][][][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

[]	[]	[]	[]	[]

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

[][]	[][]	[][]
Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

[][]	[][]	[][]
Day	Month	Year

Please PRINT Name

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience <i>(Please print clearly)</i>		→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	Day Month Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (<i>maximum</i>)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) <i>Please specify</i> _____ ☐ Another condition (eg, condition under study, intercurrent illness) <i>Please specify</i> _____ ☐ Another drug <i>Please specify</i> _____
Corrective Therapy <i>If 'Yes', record details in the Concomitant Medication or Medical Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

[]	[]	[]	[]	[]

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

[][]	[][]	[][]
Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

Please PRINT Name

[][]	[][]	[][]
Day	Month	Year

Protocol	Centre Number	Patient Number	Patient Initials												
207499/040	<table border="1"><tr><td></td><td></td><td></td></tr></table>				<table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	<table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>				
0	0	0	0	0											

CONFIDENTIAL



PROTOCOL 207499/040

BOOK 16 : GENERIC VISIT

**A MULTICENTRE, OPEN-LABEL EXTENSION STUDY TO EVALUATE
THE SAFETY, TOLERABILITY AND EFFICACY OF ORAL SB 207499
(15mg TWICE DAILY) IN PATIENTS WITH CHRONIC OBSTRUCTIVE
PULMONARY DISEASE (COPD)**

GENERAL INSTRUCTIONS

- Write clearly in capital letters using a black ball point pen and press firmly so that all copies are legible
- Do not write in shaded areas
- Answer ALL questions on every page
- Enter "N/A" if information requested is not available
- Initial and date all changes, additions or deletions. Use a single pen stroke to remove an incorrect entry
- Enter the patient initials on all pages on which information has been entered and the patient number and centre number where required
- Do not enter additional data/information after the set of CRF pages has been split/separated
- The cover flap or plastic writing board should be used to divide each set of pages before writing on them with a ball point pen

DATE

Please use the following three-letter abbreviations for the months

January	JAN
February	FEB
March	MAR
April	APR
May	MAY
June	JUN
July	JUL
August	AUG
September	SEP
October	OCT
November	NOV
December	DEC

e.g.

0	1	J	A	N	0	0
Day		Month			Year	

 = 1st January 2000

TIME

Unless specified otherwise, please use the 24 hour clock

e.g.

1	5	3	0
24hr:min			

 = 3.30 p.m

PATIENT INITIALS

Please use the following format:

e.g.

ROUTE KEY FOR PRIOR/CONCOMITANT MEDICATION PAGE

PO = By mouth	SL = Sublingual	TD = Transdermal
IV = Intravenous	IT = Intrathecal	IH = Inhaled
IM = Intramuscular	VA = Vaginal	SC = Subcutaneous
IAR = Intra-arterial	NA = Nasal	PR = Rectal
TO = Topical	IA = Intra-articular injection	ID = Intradermal

**SUMMARY CHART OF STUDY PROCEDURES (OPEN BOXES)
PROTOCOL SB 207499/040**

Mark open boxes to confirm that each procedure has been completed.

Procedures	12 Weekly Visit	24 Weekly Visit	48 Weekly Visit	Withdrawal or Stopping Study
Quality of Life Assessment: SGRQ				
Quality of Life Assessment: SF-36				
Physical (Including Respiratory) Examination				
COPD Exacerbation assessment/Healthcare Ut.				
Diary Card Review ¹				
Adverse Experiences ²				
Concomitant Medication				
Medical Procedures				
Study Medication compliance				
Smoking Status				
Pulmonary Rehabilitation Program				
Laboratory Tests				
Pregnancy Test ³				
Overall Breathlessness (Modified Borg)				
Vital Signs (BP, HR)				
Resting 12-Lead ECG				
Exercise Tolerance Test - 6 Minute Walk				
Post Exercise Breathlessness				
Pulmonary Function Tests ⁴				
Orthostatic Blood pressure and Heart Rate ⁵				
Faecal Occult Blood ⁶				
Dispense or re-dispense Open-Label Medication				
Study Continuation / Withdrawal				

¹ **A Diary Card is issued at each visit. The patient will use the Diary Card to record if they feel different since the previous visit.**

² **Patients will be assessed for GI AEs at every visit.**

³ **Serum pregnancy test for female patients of child bearing potential. Urine test only is done at Follow-Up Visit.**

⁴ **To include FEV₁, FEV₆, FVC, FEF₂₅₋₇₅, FEF₇₅, and PEFR.**

⁵ **Orthostatic blood pressure and heart rate are measured at 48 weekly intervals. Also at Early Withdrawal.**

⁶ **Faecal occult blood is measured at 48 weekly intervals. Also at Early Withdrawal.**

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Protocol	Centre Number	Patient Number	Patient Initials		
207499/040					

MODULE 50

Please do not split modules

Module 50 : Generic Visit, Adverse Experiences, Conmeds, Medical Procedures, COPD Exacerbations, Resource Utilisation, Continuation/Withdrawal

CRF Pages 700 - 730

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

At 24 and 48 Weekly Visits :
SGRQ
SF36

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Protocol	Centre Number	Patient Number	Patient Initials	Visit Date	Enter Visit Number below
207499/040		0 0 0 0 0		Day Month Year 	

VISIT DETAILS

Which Visit is this ?

Visit	Week	Mark Box
15	48 (48)	☐
18	60	☐
21	72 (24)	☐
24	84	☐
27	96 (48)	☐
30	108	☐
33	120 (24)	☐

Visit	Week	Mark Box
36	132	☐
37	144 (48)	☐
38	156	☐
39	168	☐
40	180	☐
41	192	☐
42	204	☐

(24) = This is a "24 Week Interval", please complete assessments scheduled for 24 weekly visits (p708)

(48) = This is a "48 Week Interval", please complete assessments scheduled for 48 weekly visits (p708 and p709)

PRESENTATION TO CLINIC

Record time of presentation to clinic

24hr:min

Note: Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.

Record the date and time of the patient's last dose of short-acting beta₂ agonist

Day Month Yr 24hr:min
Record the date and time of the patient's last dose of long-acting beta₂ agonist

Day Month Yr 24hr:min

Record the date and time of the patient's last dose of anticholinergic

Day Month Yr 24hr:min

Has the patient smoked within the past 2 hours?

☐ No☐ Yes → If 'Yes' please record time

24hr:min
ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

If this is a 24 weekly visit, or 48 weekly visit, or if the patient is withdrawing from the study, please ask the patient to complete the St. George's Hospital Respiratory Questionnaire and SF-36 before any further procedures are carried out (p708).

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Protocol		Patient Number	Patient Initials		Enter Visit Number below
207499/040		0 0 0 0 0			

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of exacerbation (maximum intensity)	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages (page 726).

RESOURCE UTILISATION FOR COPD EXACERBATIONS

If the patient has received any COPD exacerbation related medical care since the previous visit, please complete the COPD Resource Utilisation section at the back of this module (page 728).

DIARY CARD REVIEW

Review the diary card for illegible/incomplete entries **in the presence of the patient**

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question (page 712).

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module (page 716).

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Protocol		Patient Number	Patient Initials		Enter Visit Number below
207499/040		0 0 0 0 0			

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD Exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)

Date and time of last dose of study medication prior to the study visit

Day	Month	Yr	24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
210					

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤ 120%?

☐ No →

If 'No' please check the % compliance at the previous visit. If compliance was not ≥ 80% and ≤ 120% at the last visit, please withdraw the patient. Please complete **all** assessments at this Visit (i.e. complete those for 24 and 48 week intervals even if this is not one of them).

☐ Yes

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Protocol		Patient Number	Patient Initials		Enter Visit Number below
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SMOKING STATUS

Does the patient currently smoke?

☐ No☐ Yes → If 'Yes' please record the average number of cigarettes per day :

PULMONARY REHABILITATION PROGRAMME

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit?

☐ No☐ Yes**LABORATORY TESTS**

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential). Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date

Day	Month	Yr	

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below

Attach label here

Are there any **clinically significant worsenings** since the previous visit?☐ No☐ Yes → If 'Yes' please record the details in the Adverse Experience section at the back of this module.

Place the Quest laboratory report in the plastic wallet at the back of this module

URINALYSIS

Please perform urinalysis using the dipstick provided by Quest and record the results in the patient notes.

Urine Sample Date

Day	Month	Yr	

Are the dipstick results negative?

☐ No → If 'No' please send the sample to Quest for microscopy☐ YesAre there any **clinically significant worsenings** since the previous visit on the Quest report?☐ No☐ Yes → If 'Yes' please record the details in the Adverse Experience section at the back of this module.

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Protocol		Patient Number	Patient Initials		Enter Visit Number below
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PREGNANCY TEST

Is the patient a female of child-bearing potential?

☐ No☐ Yes → *If 'Yes' please request a pregnancy test on the Quest requisition form.*

Is the patient pregnant?

☐ No☐ Yes → *If 'Yes' please withdraw the patient from the study, enter details in the Adverse Experience section. Complete the Early Withdrawal Visit (found in a separate book).***OVERALL BREATHLESSNESS ASSESSMENT**

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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Protocol		Patient Number	Patient Initials		Enter Visit Number below
207499/040		0 0 0 0 0			

INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed:

Day Month Yr

Were any clinically significant changes noted since the last visit?

☐ No

☐ Yes → ☐ Improvement

☐ Worsening →

Enter details in the Adverse Experience section at the back of this module.

Place the ECG trace in the plastic wallet at the back of this module.

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EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes. If the patient was too ill to attempt the test, please mark the 'Yes' box and enter 0 for distance walked.

☐ No

☐ Yes → If 'Yes', Distance walked Metres

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

POST-EXERCISE BREATHLESSNESS (Immediately after the patient completes the exercise tolerance)
Heart Rate beats/min
Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

- 0 Nothing at all
- 1 Very, very slight (just noticeable)
- 2 Very slight
- 3 Moderate
- 4 Somewhat severe
- 5 Severe
- 6
- 7 Very severe
- 8
- 9 Very, very severe (almost maximal)
- 10 Maximal

Post-exercise breathlessness score

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Protocol		Patient Number	Patient Initials		Enter Visit Number below
207499/040		0 0 0 0 0			

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise tolerance test (rest for at least 10 minutes) before performing the pulmonary function tests.

PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and/or anticholinergic medications and/or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

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Protocol		Patient Number	Patient Initials		Enter Visit Number below
207499/040		0 0 0 0 0			

ASSESSMENTS DONE AT 24/48 WEEKLY VISITS AND FOR WITHDRAWALS/STOPPING

Complete the assessments below at 24 week intervals (i.e. Visits 15, 21, 27, 33, 37 etc) or for patients who are withdrawing early from the study or stopping the study because the product has been registered or because the sponsor has terminated the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes → If 'Yes' record details in the Adverse Experience section at the back of this module.

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Protocol		Patient Number	Patient Initials		Enter Visit Number below
207499/040		0 0 0 0 0			

ASSESSMENTS DONE AT 48 WEEK INTERVALS AND FOR WITHDRAWALS / STOPPING

Complete the assessments below at 48 week intervals (i.e. at visits 15, 27, 37) or for patients who are withdrawing early from the study or stopping the study because the product has been registered or because the sponsor has terminated the study.

VITAL SIGNS - ORTHOSTATIC CHANGE**1st Measurement: After 5 Minutes Supine**

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min

Are there any clinically significant worsenings since the previous assessment?

☐ No

☐ Yes → If 'Yes' record details in the Adverse Experience section at the back of this module.
FAECAL OCCULT BLOOD TEST - RESULTS

Record the results of the faecal occult blood tests performed between this visit and the previous visit.

Test	Date of Collection Day Mth Yr	Was the faecal occult blood test positive ?
1		☐ No ☐ Yes
2		☐ No ☐ Yes
3		☐ No ☐ Yes

Are these findings clinically significant ?

☐ No

☐ Yes → If 'Yes' record details in the Adverse Experiences section at the back of this module.

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Protocol		Patient Number	Patient Initials		Enter Visit Number below
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STUDY MEDICATION LABEL

Issue the patient either three bottles of 70 tablets or one bottle of 210 tablets of open-label study medication. Attach the tear-off label(s) from the study medication bottles dispensed at this visit in the spaces below. Record the start date in the Study Medication Record section in the next visit.

Attach study medication
label here

Attach study medication
label here

Attach study medication
label here

Give the patient the first dose of study medication with food and record the date and time of administration below.

Date and time of administration

Day	Month	Yr	24hr	:	min		

FAECAL OCCULT BLOOD TEST - INSTRUCTIONS

If the next visit is at a 48 - weekly interval (i.e. if the next visit is visit 27 (week 96) or visit 37 (week 144) or if patient is withdrawing issue the patient three Haemoccult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples in the week prior to the next visit (or Follow-Up visit) and return the kits at the next visit.

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Protocol		Patient Number	Patient Initials		Enter Visit Number below
207499/040		0 0 0 0 0			

INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐ No →

If 'No' please complete all assessments at this visit (i.e. including those for 24 or 48 week intervals) and issue the patient three Haemoccult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-Up Visit. Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return in 7 +/- 3 days for a Follow-Up Visit.

☐ Yes →

If 'Yes' please:

- *Issue a new diary card. Remind the patient to record if they feel differently since starting the study*
- *Ask the patient to return for the next visit in 12 weeks (84 days) + / - 6 days.*
- **Remind the patient:**
 - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*
 - ii **not** *to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*
 - iii *to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonists (long-acting) for **12 hours** before the next visit.*
 - iv *to refrain from smoking for **2 hours** immediately preceding the visit.*
 - v *to bring back at the next visit any remaining study medication or study medication containers and the diary card.*
 - vi *to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.*
 - vii *to return Faecal Occult Blood Test kits at the next visit, if issued at this visit.*

ADVERSE EXPERIENCES (Non-serious)**DEFINITIONS****INTENSITY (Maximum)**

<i>MILD</i>	<i>Adverse experience which is easily tolerated</i>
<i>MODERATE</i>	<i>Adverse experience sufficiently discomforting to interfere with daily activities</i>
<i>SEVERE</i>	<i>Adverse experience which prevents normal everyday activities</i>

RELATIONSHIP TO INVESTIGATIONAL DRUG

<i>NOT RELATED</i>	<i>The adverse experience is definitely not related to the test drug</i>
<i>UNLIKELY</i>	<i>There are other more likely causes and the drug is not suspected as a cause</i>
<i>SUSPECTED (REASONABLE POSSIBILITY)</i>	<i>A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug</i>
<i>PROBABLE</i>	<i>There probably is a direct cause and effect relationship between the adverse experience and the study drug</i>

SERIOUS ADVERSE EXPERIENCE (SAE)

An SAE is any event which is :-

- 1 - fatal
- 2 - life threatening
- 3 - disabling/incapacitating
- 4 - results in hospitalisation (excluding elective surgery or routine clinical procedures)
- 5 - prolongs a hospital stay
- 6 - associated with congenital abnormality
- 7 - cancer
- 8 - associated with overdose
- 9 - In addition any event which the investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug should be reported as a serious event

IF AN SAE OCCURS, PLEASE GO TO SAE SECTION IMMEDIATELY AND FOLLOW THE INSTRUCTIONS GIVEN THERE

Use each form for a maximum of two experiences

PLEASE REMEMBER ALL QUESTIONS ON ADVERSE EXPERIENCES FORM SHOULD BE COMPLETED

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Protocol 207499/040	Centre Number [][][]	Patient Number 0 0 0 0 0	Patient Initials [][][][]		Enter Visit Number below [][]

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous module?" Provide the diagnosis, **not** symptoms, where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbations section

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no adverse experiences occurred since the previous module, please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	[][][] Day Month Yr [][] 24hr:min	[][][] Day Month Yr [][] 24hr:min
End Date and Time (If ongoing please leave blank)	[][][] Day Month Yr [][] 24hr:min	[][][] Day Month Yr [][] 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes [][] ☐ Constant	☐ Intermittent → No. of episodes [][] ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No

Investigator's Signature _____ Date : [][][] Day Month Yr

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		Enter Visit Number below

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous module?" Provide the diagnosis, **not** symptoms, where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbations section

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no further adverse experiences or changes in adverse experiences occurred since the previous module, please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		Enter Visit Number below

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous module?" Provide the diagnosis, **not** symptoms, where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbations section

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no further adverse experiences or changes in adverse experiences occurred since the previous module, please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		Enter Visit Number below

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous module?" Provide the diagnosis, **not** symptoms, where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbations section

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no further adverse experiences or changes in adverse experiences occurred since the previous module, please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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Protocol 207499/040	Centre Number <table border="1"><tr><td></td><td></td><td></td></tr></table>				Patient Number <table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						Enter Visit Number below <table border="1"><tr><td></td><td></td></tr></table>		
0	0	0	0	0															

CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the previous module.
(Please write using BLOCK CAPITALS).

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

☐ No concomitant medication changes since the previous module

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experience section using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the new start and end date.

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)				
					Day	Mth	Yr	Day	Mth	Yr		
For SB												
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* For Route, see tab for acceptable abbreviations.												

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Protocol	Centre Number	Patient Number	Patient Initials		Enter Visit Number below
207499/040					

CONCOMITANT MEDICATION - Continued

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experience section using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the new start and end date.

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)			
					Day	Mth	Yr	Day	Mth	Yr	
											☐
For SB											
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* For Route, see tab for acceptable abbreviations.											

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		Enter Visit Number below

MEDICAL PROCEDURES - (Excluding treatment for COPD Exacerbations)

Do not record procedures used to treat COPD exacerbations here, record them in the COPD Exacerbations section.

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed since the previous module?

☐ No

☐ Yes → If 'Yes', please record details below using standard medical terminology (Please print clearly)

All indications for procedures should be recorded in the Adverse Experience section

Procedure	Indication	Procedure Start Date			Procedure End Date		
		Day	Mth	Yr	Day	Mth	Yr
For SB							
For SB							
For SB							
For SB							
For SB							
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For SB							

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		Enter Visit Number below

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.

All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages**

If no COPD Exacerbations since the previous module please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome If patient died, STOP: go to the COPD SAE section and follow instructions given there ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____ Date : Day Month Yr		

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		Enter Visit Number below

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.

All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages**

If no further COPD exacerbations or changes to COPD exacerbations have occurred since the previous module please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome If patient died, STOP: go to the COPD SAE section and follow instructions given there ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		Enter Visit Number below

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.

All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages**

If no further COPD exacerbations or changes to COPD exacerbations have occurred since the previous module please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to the COPD SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____ Date : Day Month Yr		

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)**SAEs MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS****COMPLETE THE SAE PAGES OPPOSITE**

Please complete these pages as fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Experience Course' blank and update it later

SIGN AND DATE THE SAE PAGE**PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE**

- Demography
- Significant Medical/Surgical History and Physical Examination
- Study Medication Record
- Concomitant Medication
- Form D (if applicable)

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE

(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO:

Your local SB CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local SB CRA/Medical monitor within 24 hours

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Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date	Enter Visit Number below
207499/040		0 0 0 0 0		Day Month Year 	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

Person Reporting SAE (Please print clearly) _____		AEGIS Number
Serious Adverse Experience (Please print clearly)	COPD Exacerbation	→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	
Outcome If patient died, please complete Form D ←	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) Please specify _____ ☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____ ☐ Another drug Please specify _____
Corrective Therapy If 'Yes', record details in the COPD Medication or Procedures section ←	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]	SB Receipt Date Day Month Year [][][][][][]	Enter Visit Number below [][]

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)**Relevant Laboratory Data**

Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

[][][][][]

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

[][][]	[][][]	[][][]
Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

[][][]	[][][]	[][][]
Day	Month	Year

Please PRINT Name

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Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date	Enter Visit Number below
207499/040		0 0 0 0 0		Day Month Year 	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

Person Reporting SAE (Please print clearly) _____		AEGIS Number
Serious Adverse Experience (Please print clearly)	COPD Exacerbation	→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	
Outcome If patient died, please complete Form D ←	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) Please specify _____ ☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____ ☐ Another drug Please specify _____
Corrective Therapy If 'Yes', record details in the COPD Medication or Procedures section ←	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date	Enter Visit Number below						
207499/040		0 0 0 0 0		<table border="1"> <tr> <th>Day</th> <th>Month</th> <th>Year</th> </tr> <tr> <td> </td> <td> </td> <td> </td> </tr> </table>	Day	Month	Year				
Day	Month	Year									

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range						
	<table><tr><td> </td><td> </td><td> </td></tr><tr><td>Day</td><td>Month</td><td>Yr</td></tr></table>				Day	Month	Yr			
Day	Month	Yr								
	<table><tr><td> </td><td> </td><td> </td></tr><tr><td>Day</td><td>Month</td><td>Yr</td></tr></table>				Day	Month	Yr			
Day	Month	Yr								
	<table><tr><td> </td><td> </td><td> </td></tr><tr><td>Day</td><td>Month</td><td>Yr</td></tr></table>				Day	Month	Yr			
Day	Month	Yr								
	<table><tr><td> </td><td> </td><td> </td></tr><tr><td>Day</td><td>Month</td><td>Yr</td></tr></table>				Day	Month	Yr			
Day	Month	Yr								

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

Day	Month	Year

Please PRINT Name

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Protocol 207499/040	Centre Number [][][]	Patient Number 0 0 0 0 0	Patient Initials [][][][]		Enter Visit Number below [][]

MEDICATION FOR COPD EXACERBATIONSHas the patient taken any medication for **COPD exacerbations** since the previous module?☐ No☐ Yes*If 'Yes', please record details below*

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)		
					Day	Mth	Yr	Day	Mth	Yr
				COPD EXACERBATION	[][][]	[][][]	[][][]	[][][]	[][][]	[]
For SB										
				COPD EXACERBATION	[][][]	[][][]	[][][]	[][][]	[][][]	[]
For SB										
				COPD EXACERBATION	[][][]	[][][]	[][][]	[][][]	[][][]	[]
For SB										
				COPD EXACERBATION	[][][]	[][][]	[][][]	[][][]	[][][]	[]
For SB										
				COPD EXACERBATION	[][][]	[][][]	[][][]	[][][]	[][][]	[]
For SB										
				COPD EXACERBATION	[][][]	[][][]	[][][]	[][][]	[][][]	[]
For SB										
				COPD EXACERBATION	[][][]	[][][]	[][][]	[][][]	[][][]	[]
For SB										
				COPD EXACERBATION	[][][]	[][][]	[][][]	[][][]	[][][]	[]
For SB										
* For Route, see tab for acceptable abbreviations.										

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		Enter Visit Number below

MEDICAL PROCEDURES FOR COPD EXACERBATIONS

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since the previous module?

☐ No

☐ Yes → If 'Yes', please record details below using standard medical terminology

Procedure	Indication	Procedure Start Date			Procedure End Date		
		Day	Mth	Yr	Day	Mth	Yr
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							
	COPD EXACERBATION						
For SB							

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Protocol 207499/040	Centre Number [][][]	Patient Number 0 0 0 0 0	Patient Initials [][][][]		Enter Visit Number below [][]

HEALTHCARE RESOURCE UTILISATION FOR COPD EXACERBATIONS

Complete this form for any **COPD exacerbation related medical care** the patient received since the previous module

Physician Visits (i.e., COPD care excluding scheduled protocol visits)

☐ There were no physician visits since the previous module

Date of Visit			Reason for Visit
Day	Mth	Yr	
[][][][][]			
[][][][][]			
[][][][][]			
[][][][][]			
[][][][][]			
[][][][][]			
[][][][][]			
[][][][][]			

Emergency Room (ER)/Urgent Care Visits/Casualty Department Procedures (i.e., lung surgery)

☐ There were no Emergency Room/Urgent Care Visits/Casualty Department Procedures since previous module

Date of Visit			Reason for Visit		Patient Admitted from ER?	
					Yes	No
Day	Mth	Yr				
[][][][][]					☐	☐
[][][][][]					☐	☐
[][][][][]					☐	☐
[][][][][]					☐	☐
[][][][][]					☐	☐
[][][][][]					☐	☐
[][][][][]					☐	☐

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Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]		Enter Visit Number below [][]

HEALTHCARE RESOURCE UTILISATION FOR COPD EXACERBATIONS - (cont)

Hospitalisations (also record details of any hospitalisation in the Serious Adverse Experience - COPD Exacerbation section)

☐ There were no hospitalisations since the previous module

Date of Admission Day Mth Yr	Date of Discharge Day Mth Yr	Reason for Admission
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	

Intensive Care Unit (ICU) stays (did the patient stay in the ICU during any of the above hospitalisations?)

☐ There were no ICU stays since previous module

Date Admitted to ICU Day Mth Yr	Date Discharged from ICU Day Mth Yr	Reason for ICU Admission
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	

Lost Work Days (i.e., days patient missed work due to COPD excluding scheduled protocol visits)

☐ There were no lost work days since the previous module

Stop Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	
[][][][][]	[][][][][]	

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Protocol	Centre Number	Patient Number	Patient Initials		Enter Visit Number below
207499/040		0 0 0 0 0			

STUDY CONTINUATION/WITHDRAWAL

Is the patient continuing in the study?

☐ Yes☐ No →If 'No' please mark the **primary** cause of withdrawal and enter the date of the final visit and the date of the final dose[1] ☐ Adverse experience (complete AE or SAE section)[2] ☐ Insufficient therapeutic effect[3] ☐ Protocol deviation (including non-compliance)[4] ☐ Lost to follow-up[5] ☐ Other - specify: _____

Date of Final Visit

Day	Month	Yr	

Date of Final dose

Day	Month	Yr	

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data on this case report form and that all information is complete and accurate.

Investigator's Signature _____ Date

Day	Month	Yr	

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)

SAEs MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS

COMPLETE THE SAE PAGES OPPOSITE

Please complete these pages as fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Experience Course' blank and update it later

SIGN AND DATE THE SAE PAGE**PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE**

- Demography
- Significant Medical/Surgical History and Physical Examination
- Study Medication Record
- Medical Procedures
- Concomitant Medication
- Form D (if applicable)

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE

(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO:

Your local SB CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local SB CRA/Medical monitor within 24 hours

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Protocol	Centre Number	Patient Number	Patient Initials		
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MOD51 & MOD52 - SERIOUS ADVERSE EXPERIENCES

MOD51 & MOD52	Serious Adverse Experiences
MOD51 :	731, 732
MOD52 :	733, 734

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Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date	Enter Visit Number below
207499/040		0 0 0 0 0		Day Month Year 	

SERIOUS ADVERSE EXPERIENCE (SAE)

Person Reporting SAE (Please print clearly) _____		AEGIS Number
Serious Adverse Experience (Please print clearly)		→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	
Outcome If patient died, please complete Form D	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) Please specify _____ ☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____ ☐ Another drug Please specify _____
Corrective Therapy If 'Yes', record details in the Concomitant Medication or Medical Procedures section	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date	Enter Visit Number below						
207499/040		0 0 0 0 0		<table border="1"> <tr> <th>Day</th> <th>Month</th> <th>Year</th> </tr> <tr> <td> </td> <td> </td> <td> </td> </tr> </table>	Day	Month	Year				
Day	Month	Year									

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	DayMonthYr			
	DayMonthYr			
	DayMonthYr			
	DayMonthYr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

Day	Month	Year

Please PRINT Name

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Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date	Enter Visit Number below
207499/040		0 0 0 0 0		Day Month Year 	

SERIOUS ADVERSE EXPERIENCE (SAE)

Person Reporting SAE (Please print clearly) _____		AEGIS Number
Serious Adverse Experience (Please print clearly)		→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	
Outcome If patient died, please complete Form D	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) Please specify _____ ☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____ ☐ Another drug Please specify _____
Corrective Therapy If 'Yes', record details in the Concomitant Medication or Medical Procedures section	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Page	734

Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date	Enter Visit Number below
207499/040		0 0 0 0 0		Day Month Year	

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

Day	Month	Year

Please PRINT Name

Protocol	Centre Number	Patient Number	Patient Initials
207499/040		0 0 0 0 0	

CONFIDENTIAL



PROTOCOL 207499/040

BOOK 17 : VISITS 33 AND 34 (WEEKS 120 AND 124)

**A MULTICENTRE, OPEN-LABEL EXTENSION STUDY TO EVALUATE
THE SAFETY, TOLERABILITY AND EFFICACY OF ORAL SB 207499
(15mg TWICE DAILY) IN PATIENTS WITH CHRONIC OBSTRUCTIVE
PULMONARY DISEASE (COPD)**

GENERAL INSTRUCTIONS

- Write clearly in capital letters using a black ball point pen and press firmly so that all copies are legible
- Do not write in shaded areas
- Answer ALL questions on every page
- Enter "N/A" if information requested is not available
- Initial and date all changes, additions or deletions. Use a single pen stroke to remove an incorrect entry
- Enter the patient initials on all pages on which information has been entered and the patient number and centre number where required
- Do not enter additional data/information after the set of CRF pages has been split/separated
- The cover flap or plastic writing board should be used to divide each set of pages before writing on them with a ball point pen

DATE

Please use the following three-letter abbreviations for the months

January	JAN
February	FEB
March	MAR
April	APR
May	MAY
June	JUN
July	JUL
August	AUG
September	SEP
October	OCT
November	NOV
December	DEC

e.g.

0	1	J	A	N	9	9
Day		Month			Year	

 = 1st January 1999

TIME

Unless specified otherwise, please use the 24 hour clock

e.g.

1	5	3	0
24hr:min			

 = 3.30 p.m

PATIENT INITIALS

Please use the following format:

e.g.

ROUTE KEY FOR PRIOR/CONCOMITANT MEDICATION PAGE

PO = By mouth	SL = Sublingual	TD = Transdermal
IV = Intravenous	IT = Intrathecal	IH = Inhaled
IM = Intramuscular	VA = Vaginal	SC = Subcutaneous
IAR = Intra-arterial	NA = Nasal	PR = Rectal
TO = Topical	IA = Intra-articular injection	ID = Intradermal

**SUMMARY CHART OF STUDY PROCEDURES (OPEN BOXES)
PROTOCOL SB 207499/040**

Mark open boxes to confirm that each procedure has been completed.

Procedures	Visit 33 Week 120	Visit 34 Week 124
Signed written informed consent		
Study Medication compliance		
Concomitant Medication		
Diary Card Review ⁷		
Adverse Experiences ⁸		
COPD Exacerbation assessment/Healthcare Ut.		
Physical (Including Respiratory) Examination		
Resting 12-Lead ECG		
Vital Signs (BP, HR) ³		
Overall Breathlessness (Modified Borg)		
Exercise Tolerance Test - 6 Minute Walk		
Post Exercise Breathlessness		
Pulmonary Function Tests ⁴		
Laboratory Tests ⁵		
Pregnancy Test ⁶		
Quality of Life Assessment: SGRQ		
Quality of Life Assessment: SF-36		
Dispense or re-dispense Open-Label Medication		
Study Continuation / Withdrawal		

³ **Orthostatic blood pressure and heart rate are measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal.**

⁴ **To include FEV₁, FEV₆, FVC, FEF₂₅₋₇₅, FEF₇₅, and PEFR.**

⁵ **Faecal occult blood is measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal. Baseline measure is taken from last FOB in Study 042 or Study 091**

⁶ **Serum pregnancy test for female patients of child bearing potential. Urine test only is done at Follow-Up Visit.**

⁷ **A Diary Card is issued at each visit. The patient will use the Diary Card to record if they feel different since the previous visit.**

⁸ **Patients will be assessed for GI AEs at every visit.**

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Protocol	Centre Number	Patient Number	Patient Initials		
207499/040		0 0 0 0 0			

MODULE 56*Please do not split modules*

Module 56 : Visit 33 (Week 120) and Visit 34 (Week 124), Adverse Experiences, Conmeds, Medical Procedures, COPD Exacerbations, Resource Utilisation, Continuation/Withdrawal

CRF Pages 787 - 828

Unprocessed Forms : Within this module the following occur which will generate attachments that need to be brought in-house.

Visit 33 :
SGRQ
SF36

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Page	787

Protocol	Centre Number	Patient Number	Patient Initials	Visit Date	Visit 33 Week 120
207499/040				Day Month Year 	

PRESENTATION TO CLINIC

Record time of presentation to clinic

24hr:min	

Note: Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.

Record the date and time of the patient's last dose of short-acting beta₂ agonist

Day	Month	Yr	24hr:min		

Record the date and time of the patient's last dose of long-acting beta₂ agonist

Day	Month	Yr	24hr:min		

Record the date and time of the patient's last dose of anticholinergic

Day	Month	Yr	24hr:min		

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes → If 'Yes' please record time

24hr:min	

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 33 Week 120

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	Day Month Yr	Day Month Yr	Day Month Yr	Day Month Yr
Level of exacerbation (maximum intensity)	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3	☐ Level 1 ☐ Level 2 ☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						Visit 33 Week 120

RESOURCE UTILISATION FOR COPD EXACERBATIONS

If the patient has received any COPD exacerbation related medical care since the previous visit, please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

*Review the diary card for illegible/incomplete entries **in the presence of the patient***

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD Exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a **clinically significant worsening** in the patient's physical condition since the previous examination?

☐ No

☐ Yes →

If 'Yes' record details in the Adverse Experience section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 33 Week 120

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	

Date and time of last dose of study medication prior to the study visit

[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70	[][]	[][]	[][]	[][]	[][][]

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance $\geq 80\%$ and $\leq 120\%$?

☐ No →

If 'No' please check the % compliance at the previous visit. If compliance was not $\geq 80\%$ and $\leq 120\%$ at the last visit, please withdraw the patient. Please complete the assessments for Visit 33.

☐ Yes

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 33 Week 120

SMOKING STATUS

Does the patient currently smoke?

☐ No☐ Yes → If 'Yes' please record the average number of cigarettes per day : [][]**PULMONARY REHABILITATION PROGRAMME**

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit?

☐ No☐ Yes**LABORATORY TESTS**

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential). Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date

[][]	[][]	[][]
Day	Month	Yr

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below

Attach label here

Are there any **clinically significant worsenings** since the previous visit?☐ No☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module

Place the Quest laboratory report in the plastic wallet at the back of this module

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][][]		Visit 33 Week 120

URINALYSIS

Please perform urinalysis using the dipstick provided by Quest and record the results in the patient notes.

Urine Sample Date

[][]	[][]	[][]
Day	Month	Yr

Are the dipstick results negative?

☐ No →

If 'No' please send the sample to Quest for microscopy

☐ Yes
Are there any **clinically significant worsenings** since the previous visit on the Quest report?
☐ No

☐ Yes →

If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

PREGNANCY TEST

Is the patient a female of child-bearing potential?

☐ No

☐ Yes →

If 'Yes' please request a pregnancy test on the Quest requisition form.

Is the patient pregnant?

☐ No

☐ Yes →

If 'Yes' please withdraw the patient from the study, enter details in the Adverse Experience section. Complete the Early Withdrawal Visit (found in a separate book).

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Protocol		Patient Number	Patient Initials		Visit 33 Week 120
207499/040		0 0 0 0 0			

OVERALL BREATHLESSNESS ASSESSMENT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 33 Week 120

INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed: [][] [][] [][]
Day Month Yr

Were any clinically significant changes noted since the last visit?

☐ No

☐ Yes → ☐ Improvement

☐ Worsening →

Enter details in the Adverse Experience section at the back of this module.

Place the ECG trace in the plastic wallet at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 33 Week 120

VITAL SIGNS - ORTHOSTATIC CHANGE**1st Measurement: After 5 Minutes Supine**

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the previous assessment?☐ No☐ Yes →

If 'Yes' record details in the Adverse Experience section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 33 Week 120

EXERCISE TOLERANCE TEST (6 MINUTE WALK)

Was a 6 minute walk test attempted? The distance walked should be entered even if the patient did not walk for 6 minutes. If the patient was too ill to attempt the test, please mark the 'Yes' box and enter 0 for distance walked.

☐ No

☐ Yes → If 'Yes', Distance walked [][][] Metres

Record any adverse experiences which occur during the exercise tolerance test in the Adverse Experience section at the back of this module.

POST-EXERCISE BREATHLESSNESS (Immediately after the patient completes the exercise tolerance)

Heart Rate [][][] beats/min

Breathlessness

Give the patient a copy of the following scale, ask them the following question and record the answer below.

"How short of breath do you feel right now?"

Please rate your overall breathlessness on a scale of 0 to 10, according to the scale shown below. Your response is not limited to whole numbers (for example, 3.7, 5.5, etc., are acceptable).

- 0 Nothing at all
- 1 Very, very slight (just noticeable)
- 2 Very slight
- 3 Moderate
- 4 Somewhat severe
- 5 Severe
- 6
- 7 Very severe
- 8
- 9 Very, very severe (almost maximal)
- 10 Maximal

Post-exercise breathlessness score

[][]	.	[]

INVESTIGATOR INSTRUCTIONS

The patient must be completely rested after the exercise tolerance test (rest for at least 10 minutes) before performing the pulmonary function tests.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 33 Week 120

PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and/or anticholinergic medications and/or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

STUDY MEDICATION LABEL

Issue the patient one bottle of open-label study medication (70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

Attach study medication
label here

Give the patient the first dose of study medication with food and record the date and time of administration below.

Date and time of administration

[][]	[][]	[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:	min	

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Protocol		Patient Number	Patient Initials		Visit 33 Week 120
207499/040		0 0 0 0 0			

INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐ No →

If 'No' please complete the assessments for Visit 33 and issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-Up Visit. Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return in 7 +/- 3 days for a Follow-Up Visit.

☐ Yes →

If 'Yes' please:

- *Issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the next visit.*
- *Issue a new diary card. Remind the patient to record if they feel differently since starting the study*
- *Ask the patient to return for the next visit in 28 + / - 6 days.*
- **Remind the patient:**
 - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*
 - ii **not** *to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*
 - iii *to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for 2 hours and beta-2 agonists (long-acting) for 12 hours before the next visit.*
 - iv *to refrain from smoking for 2 hours immediately preceding the visit.*
 - v *to bring back at the next visit any remaining study medication or study medication containers and the diary card.*
 - vi *to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.*

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Protocol 207499/040	Centre Number	Patient Number	Patient Initials	Visit Date			Visit 34 Week 124
				Day	Month	Year	
		0 0 0 0 0					

PRESENTATION TO CLINIC

Record time of presentation to clinic

 24hr:min

Note: Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.

Record the date and time of the patient's last dose of short-acting beta₂ agonist

Day	Month	Yr			

 24hr:min
Record the date and time of the patient's last dose of long-acting beta₂ agonist

Day	Month	Yr			

 24hr:min

Record the date and time of the patient's last dose of anticholinergic

Day	Month	Yr			

 24hr:min

Has the patient smoked within the past 2 hours?

☐ No☐ Yes → If 'Yes' please record time

 24hr:min
COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	<table border="1"> <tr> <td></td> <td></td> <td></td> </tr> <tr> <td>Day</td> <td>Month</td> <td>Yr</td> </tr> </table>				Day	Month	Yr	<table border="1"> <tr> <td></td> <td></td> <td></td> </tr> <tr> <td>Day</td> <td>Month</td> <td>Yr</td> </tr> </table>				Day	Month	Yr	<table border="1"> <tr> <td></td> <td></td> <td></td> </tr> <tr> <td>Day</td> <td>Month</td> <td>Yr</td> </tr> </table>				Day	Month	Yr	<table border="1"> <tr> <td></td> <td></td> <td></td> </tr> <tr> <td>Day</td> <td>Month</td> <td>Yr</td> </tr> </table>				Day	Month	Yr
Day	Month	Yr																										
Day	Month	Yr																										
Day	Month	Yr																										
Day	Month	Yr																										
Level of exacerbation (maximum intensity)	☐ Level 1	☐ Level 1	☐ Level 1	☐ Level 1																								
	☐ Level 2	☐ Level 2	☐ Level 2	☐ Level 2																								
	☐ Level 3	☐ Level 3	☐ Level 3	☐ Level 3																								

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.

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RESOURCE UTILISATION FOR COPD EXACERBATIONS

Please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

Review the diary card for illegible/incomplete entries in the presence of the patient

ADVERSE EXPERIENCES

Please complete the Adverse Experience section at the back of this module. If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

Please complete the Concomitant Medication section at the back of this module. If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD Exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 34 Week 124

FAECAL OCCULT BLOOD TEST

Record the results of the faecal occult blood tests performed between visits 33 and 34

Test	Date of Collection Day Mth Yr	Was the faecal occult blood test positive ?
1	[][][][][]	☐ No ☐ Yes
2	[][][][][]	☐ No ☐ Yes
3	[][][][][]	☐ No ☐ Yes

Are these findings clinically significant ?

☐ No

☐ Yes → If 'Yes' record details in the Adverse Experiences section at the back of this module.

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 34 Week 124

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	
[][][][][]	[][][][][]	[]	

Date and time of last dose of study medication prior to the study visit

[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance
70	[][]	[][]	[][]	[][]	[][][]

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance $\geq 80\%$ and $\leq 120\%$?

☐ No →

If 'No' please check the % compliance at the previous visit. If compliance was not $\geq 80\%$ and $\leq 120\%$ at the last visit, please withdraw the patient. Please complete the assessments for Visit 34 and the assessments for patients withdrawing or stopping the study at Visit 34, contained at the end of this visit.

☐ Yes

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SMOKING STATUS

Does the patient currently smoke?

☐ No☐ Yes → If 'Yes' please record the average number of cigarettes per day : [][]**PULMONARY REHABILITATION PROGRAMME**

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit?

☐ No☐ Yes**LABORATORY TESTS**

Please take blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential). Please refer to the instructions on the Quest shipping form and manual.

Blood Sample Date

[][]	[][]	[][]
Day	Month	Yr

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below

Attach label here

Are there any **clinically significant worsenings** since the previous visit?☐ No☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module

Place the Quest laboratory report in the plastic wallet at the back of this module

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URINALYSIS

Please perform urinalysis using the dipstick provided by Quest and record the results in the patient notes.

Urine Sample Date [][][][][][]
Day Month Yr

Are the dipstick results negative?

☐ No → If 'No' please send the sample to Quest for microscopy

☐ Yes

Are there any **clinically significant worsenings** since the previous visit on the Quest report?

☐ No

☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.

PREGNANCY TEST

Is the patient a female of child-bearing potential?

☐ No

☐ Yes → If 'Yes' please request a pregnancy test on the Quest requisition form.

Is the patient pregnant?

☐ No

☐ Yes → If 'Yes' please withdraw the patient from the study, enter details in the Adverse Experience section. Complete the Early Withdrawal Visit (found in a separate book).

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OVERALL BREATHLESSNESS ASSESSMENT

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the last visit?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed: [][] [][] [][]
Day Month Yr

Were any clinically significant changes noted since the last visit?

☐ No

☐ Yes → ☐ Improvement

☐ Worsening →

Enter details in the Adverse Experience section at the back of this module.

Place the ECG trace in the plastic wallet at the back of this module.

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PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and/or anticholinergic medications and/or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.

STUDY MEDICATION LABEL

Issue the patient one bottle of open-label study medication (70 tablets). Attach the tear-off label from the study medication bottle dispensed at this visit in the space below. Record the start date in the Study Medication Record section in the next visit.

**Attach study medication
label here**

Give the patient the first dose of study medication with food and record the date and time of administration below.

Date and time of administration

[][]	[][]	[][]	[][]	[][]	[][]
Day	Month	Yr	24hr:min		

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INSTRUCTIONS TO THE INVESTIGATOR

Is the patient continuing in the study?

☐ No →

If 'No' please complete the assessments for Visit 34 and the Assessments for Patients Withdrawing or Stopping the Study at Visit 34 contained on the following pages. Complete and fax the Withdrawal Form contained in the Withdrawal and Follow-Up Book.

☐ Yes →

If 'Yes' please:

- *Issue a new diary card. Remind the patient to record if they feel differently since starting the study*
- *Ask the patient to return for the next visit in 28 +/- 6 days.*
- *Complete the Study Continuation / Withdrawal page at the back of this module.*
- **Remind the patient:**
 - i *to take the evening dose immediately after their evening meal and to take the morning dose immediately after breakfast.*
 - ii **not** *to take the morning dose of study medication at home on the day of the next clinic visit. If, however, in exceptional circumstances the appointment has to be in the afternoon, the patient should be instructed to take the morning dose of study medication after breakfast and the visit arranged so that there is at least 8 hours between the morning dose and the visit. (eg if study medication is taken at 08:00, the visit must be 16:00 or later).*
 - iii *to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonists (long-acting) for **12 hours** before the next visit.*
 - iv *to refrain from smoking for **2 hours** immediately preceding the visit.*
 - v *to bring back at the next visit any remaining study medication or study medication containers and the diary card.*
 - vi *to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.*

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ASSESSMENTS FOR PATIENTS WITHDRAWING OR STOPPING THE STUDY

Complete the assessments below only for patients who are withdrawing early from the study or stopping the study because the product has been registered or because the sponsor has terminated the study.

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a clinically significant worsening in the patient's physical condition since the previous examination?

☐ No

☐ Yes →

If 'Yes' record details in the Adverse Experience section at the back of this module.

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FAECAL OCCULT BLOOD TEST

Issue the patient three Haemocult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the Follow-Up Visit.

VITAL SIGNS - ORTHOSTATIC CHANGE**1st Measurement: After 5 Minutes Supine**

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure (mmHg) systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]

Are there any **clinically significant worsenings** since the previous assessment?

☐ No

☐ Yes → If 'Yes' record details in the Adverse Experience section at the back of this module.

INVESTIGATOR INSTRUCTIONS

Complete the Study Continuation / Withdrawal page at the back of this book and ask the patient to return for the Follow-Up Visit in 7 +/- 3 days.

ADVERSE EXPERIENCES (Non-serious)**DEFINITIONS****INTENSITY (Maximum)**

<i>MILD</i>	<i>Adverse experience which is easily tolerated</i>
<i>MODERATE</i>	<i>Adverse experience sufficiently discomforting to interfere with daily activities</i>
<i>SEVERE</i>	<i>Adverse experience which prevents normal everyday activities</i>

RELATIONSHIP TO INVESTIGATIONAL DRUG

<i>NOT RELATED</i>	<i>The adverse experience is definitely not related to the test drug</i>
<i>UNLIKELY</i>	<i>There are other more likely causes and the drug is not suspected as a cause</i>
<i>SUSPECTED (REASONABLE POSSIBILITY)</i>	<i>A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug</i>
<i>PROBABLE</i>	<i>There probably is a direct cause and effect relationship between the adverse experience and the study drug</i>

SERIOUS ADVERSE EXPERIENCE (SAE)

An SAE is any event which is :-

- 1 - fatal
- 2 - life threatening
- 3 - disabling/incapacitating
- 4 - results in hospitalisation (excluding elective surgery or routine clinical procedures)
- 5 - prolongs a hospital stay
- 6 - associated with congenital abnormality
- 7 - cancer
- 8 - associated with overdose
- 9 - In addition any event which the investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug should be reported as a serious event

IF AN SAE OCCURS, PLEASE GO TO SAE SECTION IMMEDIATELY AND FOLLOW THE INSTRUCTIONS GIVEN THERE

Use each form for a maximum of two experiences

PLEASE REMEMBER ALL QUESTIONS ON ADVERSE EXPERIENCES FORM SHOULD BE COMPLETED

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ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous module?" Provide the diagnosis, **not** symptoms, where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbations section

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no adverse experiences occurred since the previous module, please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous module?" Provide the diagnosis, **not** symptoms, where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbations section

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no further adverse experiences or changes in adverse experiences occurred since the previous module, please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Have you felt different in any way since starting the treatment or since the previous module?" Provide the diagnosis, **not** symptoms, where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbations section

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the Serious Adverse Experience (SAE) section (See opposite for definitions of an SAE).

If no further adverse experiences or changes in adverse experiences occurred since the previous module, please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the previous module.
(Please write using BLOCK CAPITALS).

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

☐ No concomitant medication changes since the previous module

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experience section using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the new start and end date.

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)			
					Day	Mth	Yr	Day	Mth	Yr	
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* For Route, see tab for acceptable abbreviations.											

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CONCOMITANT MEDICATION - Continued

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experience section using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the new start and end date.

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)			
					Day	Mth	Yr	Day	Mth	Yr	
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* For Route, see tab for acceptable abbreviations.											

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MEDICAL PROCEDURES - (Excluding treatment for COPD Exacerbations)

Do not record procedures used to treat COPD exacerbations here, record them in the COPD Exacerbations section.

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed since the previous module?

☐ No

☐ Yes → If 'Yes', please record details below using standard medical terminology (Please print clearly)

All indications for procedures should be recorded in the Adverse Experience section

Procedure	Indication	Procedure Start Date			Procedure End Date																										
		Day	Mth	Yr	Day	Mth	Yr																								
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SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number	Patient Initials		
207499/040		0 0 0 0			

An exacerbation of COPD is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy. All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages**

If no COPD Exacerbations since the previous module please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	Day Month Yr 24hr:min	Day Month Yr 24hr:min
Outcome If patient died, STOP: go to the COPD SAE section and follow instructions given there	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____ Date : Day Month Yr		

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Page	818

Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.

All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages**

If no further COPD exacerbations or changes to COPD exacerbations have occurred since the previous module please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome If patient died, STOP: go to the COPD SAE section and follow instructions given there ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Month Yr	

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Page	819

Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy.

All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages**

If no further COPD exacerbations or changes to COPD exacerbations have occurred since the previous module please sign the form below and mark this box. ☐

Adverse Experience (please print clearly)	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	 Day Month Yr 24hr:min
Outcome <i>If patient died, STOP: go to the COPD SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures sections if appropriate ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____ Date : Day Month Yr		

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)**SAEs MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS****COMPLETE THE SAE PAGES OPPOSITE**

Please complete these pages as fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Experience Course' blank and update it later

SIGN AND DATE THE SAE PAGE**PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE**

- Demography
- Significant Medical/Surgical History and Physical Examination
- Study Medication Record
- Concomitant Medication
- Form D (if applicable)

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE
(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO:

Your local SB CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local SB CRA/Medical monitor within 24 hours

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Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date		
207499/040				Day	Month	Year
		0 0 0 0 0				

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation

Person Reporting SAE (Please print clearly) _____		AEGIS Number
Serious Adverse Experience (Please print clearly)	COPD Exacerbation	→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	
Outcome If patient died, please complete Form D	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) Please specify _____ ☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____ ☐ Another drug Please specify _____
Corrective Therapy If 'Yes', record details in the COPD Medication or Procedures section	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]	SB Receipt Date Day Month Year [][][][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	Day Month Yr [][][][][]			
	Day Month Yr [][][][][]			
	Day Month Yr [][][][][]			
	Day Month Yr [][][][][]			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

[][][][][]

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

[][][]	[][][]	[][][]
Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

Please PRINT Name

[][][]	[][][]	[][][]
Day	Month	Year

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience <i>(Please print clearly)</i>	COPD Exacerbation	→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	 Day Month Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) <i>Please specify _____</i> ☐ Another condition (eg, condition under study, intercurrent illness) <i>Please specify _____</i> ☐ Another drug <i>Please specify _____</i>
Corrective Therapy <i>If 'Yes', record details in the COPD Medication or Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 	SB Receipt Date			
				Day 	Month 	Year 	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	 Day Month Yr			
	 Day Month Yr			
	 Day Month Yr			
	 Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

Day Month Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

Day Month Year

Please PRINT Name

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Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]		

MEDICATION FOR COPD EXACERBATIONSHas the patient taken any medication for **COPD exacerbations** since the previous module?☐ No☐ Yes → If 'Yes', please record details below

Drug Name (Trade Name Preferred)	Unit Dose (eg 500mg)	Frequency (eg bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of diagnosis)	Start Date (be as precise as possible)			End Date (or if Continuing mark box)		
					Day	Mth	Yr	Day	Mth	Yr
				COPD EXACERBATION	[][][][]	[][][][]	[][][][]	[][][][]	[][][][]	☐
For SB										
				COPD EXACERBATION	[][][][]	[][][][]	[][][][]	[][][][]	[][][][]	☐
For SB										
				COPD EXACERBATION	[][][][]	[][][][]	[][][][]	[][][][]	[][][][]	☐
For SB										
				COPD EXACERBATION	[][][][]	[][][][]	[][][][]	[][][][]	[][][][]	☐
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				COPD EXACERBATION	[][][][]	[][][][]	[][][][]	[][][][]	[][][][]	☐
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				COPD EXACERBATION	[][][][]	[][][][]	[][][][]	[][][][]	[][][][]	☐
For SB										
				COPD EXACERBATION	[][][][]	[][][][]	[][][][]	[][][][]	[][][][]	☐
For SB										
* For Route, see tab for acceptable abbreviations.										

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Protocol 207499/040	Centre Number [][][]	Patient Number 0 0 0 0 0	Patient Initials [][][][]		

MEDICAL PROCEDURES FOR COPD EXACERBATIONS

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since the previous module?

☐ No

☐ Yes → If 'Yes', please record details below using standard medical terminology

Procedure	Indication	Procedure Start Date			Procedure End Date		
		Day	Mth	Yr	Day	Mth	Yr
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
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	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							

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Protocol 207499/040	Centre Number <table border="1"><tr><td></td><td></td><td></td></tr></table>				Patient Number <table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						
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HEALTHCARE RESOURCE UTILISATION FOR COPD EXACERBATIONS

Complete this form for any **COPD exacerbation related medical care** the patient received since the previous module

Physician Visits (i.e., COPD care excluding scheduled protocol visits)

☐ There were no physician visits since the previous module

Date of Visit				Reason for Visit	
Day	Mth	Yr			
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Emergency Room (ER)/Urgent Care Visits/Casualty Department Procedures (i.e., lung surgery)

☐ There were no Emergency Room/Urgent Care Visits/Casualty Department Procedures since previous module

Date of Visit			Reason for Visit	Patient Admitted from ER?																
				Yes	No															
Day	Mth	Yr																		
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Protocol 207499/040	Centre Number <table border="1"><tr><td></td><td></td><td></td></tr></table>				Patient Number <table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						
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HEALTHCARE RESOURCE UTILISATION FOR COPD EXACERBATIONS - (cont)

Hospitalisations (also record details of any hospitalisation in the Serious Adverse Experience - COPD Exacerbation section)

☐ There were no hospitalisations since the previous module

Date of Admission Day Mth Yr	Date of Discharge Day Mth Yr	Reason for Admission										
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Intensive Care Unit (ICU) stays (did the patient stay in the ICU during any of the above hospitalisations?)

☐ There were no ICU stays since previous module

Date Admitted to ICU Day Mth Yr	Date Discharged from ICU Day Mth Yr	Reason for ICU Admission										
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Lost Work Days (i.e., days patient missed work due to COPD excluding scheduled protocol visits)

☐ There were no lost work days since the previous module

Stop Date Day Mth Yr	Stop Date Day Mth Yr	Reason for Absence										
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Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		

STUDY CONTINUATION/WITHDRAWAL

Is the patient continuing in the study?

☐ Yes☐ No →*If 'No' please mark the **primary** cause of withdrawal and enter the date of the final visit and the date of the final dose*[1] ☐ Adverse experience (complete AE or SAE section)[2] ☐ Insufficient therapeutic effect[3] ☐ Protocol deviation (including non-compliance)[4] ☐ Lost to follow-up[5] ☐ Other - specify: _____

Date of Final Visit

Day	Month	Yr

Date of Final dose

Day	Month	Yr

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data on this case report form and that all information is complete and accurate.

Investigator's Signature

Date

Day	Month	Yr

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)

SAEs MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS

COMPLETE THE SAE PAGES OPPOSITE

Please complete these pages as fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Experience Course' blank and update it later

SIGN AND DATE THE SAE PAGE**PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE**

- Demography
- Significant Medical/Surgical History and Physical Examination
- Study Medication Record
- Medical Procedures
- Concomitant Medication
- Form D (if applicable)

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE

(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO:

Your local SB CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local SB CRA/Medical monitor within 24 hours

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Protocol	Centre Number	Patient Number	Patient Initials		
207499/040		0 0 0 0 0			

MOD57 & MOD58 - SERIOUS ADVERSE EXPERIENCES

MOD57 & MOD58	Serious Adverse Experiences
MOD57 :	829, 830
MOD58 :	831, 832



SmithKline Beecham
Pharmaceuticals

Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date		
				Day	Month	Year
207499/040		0 0 0 0 0				

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience <i>(Please print clearly)</i>		→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	Day Month Yr 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	Day Month Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity <i>(maximum)</i>	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	→ Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) <i>Please specify</i> _____ ☐ Another condition (eg, condition under study, intercurrent illness) <i>Please specify</i> _____ ☐ Another drug <i>Please specify</i> _____
Corrective Therapy <i>If 'Yes', record details in the Concomitant Medication or Medical Procedures section</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

00000



Page	830

Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 	SB Receipt Date			
				Day	Month	Year	

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	 Day Month Yr			
	 Day Month Yr			
	 Day Month Yr			
	 Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

Day	Month	Year

Please PRINT Name

00000



Page	831

Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date		
207499/040				Day	Month	Year
		0 0 0 0 0				

SERIOUS ADVERSE EXPERIENCE (SAE)

Person Reporting SAE (Please print clearly) _____		AEGIS Number
Serious Adverse Experience (Please print clearly)		→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal [2] ☐ life threatening [3] ☐ disabling/incapacitating [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] ☐ hospitalisation prolonged [6] ☐ congenital abnormality [7] ☐ cancer [8] ☐ overdose [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	 Day Month Yr 24hr:min	
End Date and Time (If ongoing please leave blank)	 Day Month Yr 24hr:min	
Outcome If patient died, please complete Form D	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No If yes, did SAE recur? ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	Assessment The SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) Please specify _____ ☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____ ☐ Another drug Please specify _____
Corrective Therapy If 'Yes', record details in the Concomitant Medication or Medical Procedures section	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	

00000



Page	832

Protocol 207499/040	Centre Number [][][]	Patient Number [0][0][0][0][0]	Patient Initials [][][][]	SB Receipt Date Day Month Year [][][][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data***Please provide relevant abnormal laboratory data below*

Test	Date	Value	Units	Normal Range
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			
	[][][][][] Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

If applicable, was randomisation code broken at investigational site?

☐ No ☐ Yes

Randomisation / Study Medication Number:

[][][][][]

Investigator's Signature:

(confirming that the above data are accurate and complete)

Date

[][][]	[][][]	[][][]
Day	Month	Year

Please PRINT Name

SB Medical Monitor's Signature:

Date

[][][]	[][][]	[][][]
Day	Month	Year

Please PRINT Name

Protocol	Centre Number	Patient Number	Patient Initials
207499/040			

CONFIDENTIAL



PROTOCOL SB 207499/040

WITHDRAWAL AND FOLLOW-UP BOOK

**A MULTICENTRE, OPEN-LABEL EXTENSION STUDY
TO EVALUATE THE SAFETY, TOLERABILITY AND EFFICACY
OF ORAL SB 207499 (15mg TWICE DAILY) IN PATIENTS WITH
CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)**

GENERAL INSTRUCTIONS

- Write clearly in capital letters using a black ball point pen and press firmly so that all copies are legible
- Do not write in shaded areas
- Answer ALL questions on every page
- Enter "N/A" if information requested is not available
- Initial and date all changes, additions or deletions. Use a single pen stroke to remove an incorrect entry
- Enter the patient initials on all pages on which information has been entered and the patient number and centre number where required
- Do not enter additional data/information after the set of CRF pages has been split/separated
- The cover flap or plastic writing board should be used to divide each set of pages before writing on them with a ball point pen

DATE

Please use the following three-letter abbreviations for the months :

January	JAN
February	FEB
March	MAR
April	APR
May	MAY
June	JUN
July	JUL
August	AUG
September	SEP
October	OCT
November	NOV
December	DEC

e.g.

0	1	J	A	N	9	9
Day		Mth			Yr	

 = 1st January 1999

TIME

Unless specified otherwise, please use the 24 hour clock :

e.g.

1	5	3	0
24hr:min			

 = 3.30 p.m.

PATIENT INITIALS

Please use the following format ;

e.g. XXXXXXXXXX

ROUTE KEY FOR PRIOR/CONCOMITANT MEDICATION PAGE

PO = By mouth	SL = Sublingual	TD = Transdermal
IV = Intravenous	IT = Intrathecal	IH = Inhaled
IM = Intramuscular	VA = Vaginal	SC = Subcutaneous
IAR = Intra-arterial	NA = Nasal	PR = Rectal
TO = Topical	IA = Intra-articular injection	ID = Intradermal

SUMMARY CHART OF STUDY PROCEDURES (OPEN BOXES)
PROTOCOL SB 207499/040

Mark open boxes to confirm that each procedure has been completed.

Procedures	Early Withdrawal	Follow-Up
Signed written informed consent		
Study Medication compliance		
Concomitant Medication		
Diary Card Review ⁷		
Adverse Experiences ⁸		
COPD Exacerbation assessment/Healthcare Ut.		
Physical (Including Respiratory) Examination		²
Resting 12-Lead ECG		²
Vital Signs (BP, HR) ³		
Overall Breathlessness (Modified Borg)		
Exercise Tolerance Test - 6 Minute Walk		
Post Exercise Breathlessness		
Pulmonary Function Tests ⁴		
Laboratory Tests ⁵		²
Pregnancy Test ⁶		
Quality of Life Assessment: SGRQ		
Quality of Life Assessment: SF-36		
Dispense or re-dispense Open-Label Medication		
Study Conclusion Record		

² Only if abnormalities are present at the previous visit.

³ Orthostatic blood pressure and heart rate are measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal.

⁴ To include FEV₁, FEV₆, FVC, FEF₂₅₋₇₅, FEF₇₅, and PEFR.

⁵ Faecal occult blood is measured at 24 weeks, 48 weeks and annually thereafter. Also at Early Withdrawal. Baseline measure is taken from last FOB in Study 042 or Study 091.

⁶ Serum pregnancy test for female patients of child bearing potential. Urine test only is done at Follow-Up Visit.

⁷ A Diary Card is issued at each visit. The patient will use the Diary Card to record if they feel differently since the previous visit.

⁸ Patients will be assessed for GI AEs at every visit.



Protocol	Centre Number	Patient Number			
207499/040					

MODULE 43

MODULE 43: Early Withdrawal Visit.

CRF Pages: 649 - 658

Unprocessed forms: Within this module the following occur which will generate attachments that need to be brought in-house.

Early Withdrawal
St Georges Respiratory Questionnaire
SF36

**PATIENT WITHDRAWAL FORM
STUDY SB207499/040**

Please complete this form and fax it to the local SB monitor

To :

Fax. No. :

The following patient has been withdrawn from Study 207499/040 :

Patient Initials	Patient Number	Centre Number

Date withdrawn :

Day	Mth	Yr

Signed : _____ Date :

Day	Mth	Yr

Please print name : _____

Institution : _____



Protocol	Centre Number	Patient Number	Patient Initials	Visit Date Day Mth Yr	Early Withdrawal Visit
207499/040					

PRESENTATION TO CLINIC

Record time of presentation to clinic
24hr:min

Note : Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.

Record the date and time of the patient's last dose of short-acting beta₂ agonist
Day Mth Yr 24hr:min

Record the date and time of the patient's last dose of long-acting beta₂ agonist
Day Mth Yr 24hr:min

Record the date and time of the patient's last dose of anticholinergic
Day Mth Yr 24hr:min

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes → If 'Yes' please record time
24hr:min

ST GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE AND SF-36

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.



Protocol 207499/040		Patient Number 	Patient Initials 		Early Withdrawal Visit

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐

No

☐

Yes —► If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	Day Mth Yr	Day Mth Yr	Day Mth Yr	Day Mth Yr
Level of exacerbation (maximum intensity)	☐ Level 1	☐ Level 1	☐ Level 1	☐ Level 1
	☐ Level 2	☐ Level 2	☐ Level 2	☐ Level 2
	☐ Level 3	☐ Level 3	☐ Level 3	☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.



Protocol 207499/040		Patient Number 	Patient Initials 		Early Withdrawal Visit

RESOURCE UTILISATION FOR COPD EXACERBATIONS

If the patient has received any COPD exacerbation related medical care since the previous visit, please complete the COPD Resource Utilisation section at the back of this book.

DIARY CARD REVIEW

*Review the diary card for illegible/incomplete entries **in the presence of the patient.***

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this book. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this book.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this book.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Has there been a clinically significant worsening in the patient's physical condition since the previous examination ?

☐

No

☐

Yes



If 'Yes' record details in the Adverse Experience section at the back of this book.



Protocol 207499/040		Patient Number 	Patient Initials 		Early Withdrawal Visit

STUDY MEDICATION RECORD

Record the exact start and end dates of study medication dispensed at the previous visit. The start date should be the date of the previous visit and the end date should be when the last dose of study medication was taken. Record interruptions or changes in dose on separate lines.

Start Date Day Mth Yr	End Date Day Mth Yr	Number of tablets per dose	Frequency (e.g. bid)

Date and time of last dose of study medication prior to the study visit

Day	Mth	Yr	24hr:min

STUDY MEDICATION COMPLIANCE

Tablets Dispensed (X)	Tablets Returned (Y)	Tablets Lost (Z)	Tablets Taken (X-Y-Z)	Days Since Last Visit	% Compliance

Note: If this is a morning visit patients should not have taken the morning dose of study medication prior to this visit. If this is an afternoon visit, ≥ 8 hours must have elapsed since the last dose of study medication.

$$\% \text{ Compliance} = \frac{\text{Number of Tablets Taken}}{2 \times \text{Days Since Last Visit}} \times 100$$

Is compliance ≥ 80% and ≤ 120%?

- ☐ No
☐ Yes



Protocol 207499/040		Patient Number 	Patient Initials 		Early Withdrawal Visit

SMOKING STATUS

Does the patient currently smoke ?

☐

No

☐

Yes



If 'Yes' please record the average number of cigarettes per day :

PULMONARY REHABILITATION PROGRAMME

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit ?

☐

No

☐

Yes

LABORATORY TESTS

Please take blood samples for haematology and blood chemistry (including a beta HCG pregnancy test for females of child-bearing potential). Please refer to the instructions on the SBCL shipping form and manual.

Blood Sample Date

Day
Mth
Yr

Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below.

Attach label here

Are there any **clinically significant worsenings** since the previous visit ?

☐

No

☐

Yes



If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this book.

Place the SBCL laboratory report in the plastic wallet at the back of this book.



Protocol 207499/040		Patient Number 	Patient Initials 		Early Withdrawal Visit

URINALYSIS

Please perform urinalysis using the dipstick provided by SBCL and record the results in the patient notes.

Urine Sample Date
Day Mth Yr

Are the dipstick results negative?

- ☐ No —▶ If 'No' please send the sample to SBCL for microscopy
☐ Yes

Are there any **clinically significant worsenings** since the last visit on the SBCL report?

- ☐ No
☐ Yes —▶ If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this book.

PREGNANCY TEST

Is the patient a female of child-bearing potential ?

- ☐ No
☐ Yes —▶ If 'Yes' please request a pregnancy test on the SBCL requisition form.

Is the patient pregnant?

- ☐ No
☐ Yes —▶ If 'Yes' please enter details in the Adverse Experience section.



Protocol 207499/040		Patient Number 	Patient Initials 		Early Withdrawal Visit

INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)
/	

Are there any **clinically significant worsenings** since the last visit ?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this book.*

12 LEAD ELECTROCARDIOGRAM

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed:
Day Mth Yr

Were any clinically significant changes noted since the last visit ?

☐ No

☐ Yes → ☐ Improvement

☐ Worsening → *Enter details in the Adverse Experience section at the back of this book.*

Place the ECG trace in the plastic wallet at the back of this book.



Protocol 207499/040		Patient Number 	Patient Initials 		Early Withdrawal Visit

VITAL SIGNS - ORTHOSTATIC CHANGE

1st Measurement : After 5 Minutes Supine

Blood Pressure mmHg systolic / diastolic	Heart Rate beats/min
/	

2nd Measurement : After sitting with Legs Dependent for 1 minute

Blood Pressure mmHg systolic / diastolic	Heart Rate beats/min
/	

Are there any **clinically significant worsenings** since the previous assessment ?

☐

No

☐

Yes



If 'Yes' record details in the Adverse Experience section at the back of this book.



Protocol		Patient Number	Patient Initials		Early Withdrawal Visit
207499/040					

PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and / or anticholinergic medications and / or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐ Performed

Place the spirometry report in the plastic wallet at the back of this module.



Protocol 207499/040		Patient Number 	Patient Initials 		Early Withdrawal Visit

INSTRUCTIONS TO THE INVESTIGATOR

- Please complete the Study Conclusion page at the back of this book and ask the patient to return for the Safety Follow-up Visit in 7 +/- 2 days.
- Issue a new diary card. Remind the patient to record if they feel differently since starting the study.
- Issue the patient three Haemoccult test envelopes and three collection kits for the faecal occult blood tests. Instruct the patient to collect samples and return the kits by the next visit.
- **Remind the patient:**
 - i to refrain from taking beta-2 agonists (short-acting) or anticholinergic medications for **2 hours** and beta-2 agonist (long-acting) for **12 hours** before the next visit.
 - ii to refrain from smoking for **2 hours** immediately preceding the visit.
 - iii to bring the diary card to the next visit.
 - iv to call the investigator as soon as possible to report any gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, or vomiting) which cause them concern or interfere with their daily activities (including eating and sleeping). The investigator must complete a clinical assessment of the gastrointestinal adverse experience(s) within 24 hours of the patient reporting.



Protocol 207499/040	Centre Number <table border="1"><tr><td></td><td></td><td></td></tr></table>				Patient Number <table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>								

MODULE 44

MODULE 44: Follow-Up Visit, Adverse Experiences, Conmeds, Medical Procedures, COPD Exacerbations, Resource Utilisation.

CRF Pages: 659 - 682

Unprocessed forms: Within this module the following occur which will generate attachments that need to be brought in-house.

None



Page 659

Protocol	Centre Number	Patient Number	Patient Initials	Visit Date Day Mth Yr	Follow-Up Visit
207499/040					

PRESENTATION TO CLINIC

Record time of presentation to clinic
24hr:min

Note: Patients must wait for greater than 2 hours after short acting beta₂-agonist and / or anticholinergic administration and greater than 12 hours after the last long-acting beta₂-agonist administration before the pulmonary function tests are performed.

Record the date and time of the patient's last dose of short-acting beta₂ agonist
Day Mth Yr 24hr:min

Record the date and time of the patient's last dose of long-acting beta₂ agonist
Day Mth Yr 24hr:min

Record the date and time of the patient's last dose of anticholinergic
Day Mth Yr 24hr:min

Has the patient smoked within the past 2 hours?

☐ No

☐ Yes → If 'Yes' please record time
24hr:min

COPD EXACERBATIONS

Have there been any COPD exacerbations experienced by the patient since the last visit?

☐ No

☐ Yes → If 'Yes' please record details below.

Level 1: Acute worsening of COPD that is self-managed by the patient at home by increasing usual COPD medications (i.e., the patient does not see a doctor for this episode).

Level 2: Acute worsening of COPD that requires additional treatment (e.g. short course of oral steroids, antibiotics etc.) prescribed by a family physician or primary care doctor or as a result of a hospital outpatient visit (including a visit to the Emergency Room).

Level 3: Acute worsening of COPD that requires the patient to be admitted to the hospital for treatment.

Onset Date	 Day Mth Yr	 Day Mth Yr	 Day Mth Yr	 Day Mth Yr
Level of exacerbation (maximum intensity)	☐ Level 1	☐ Level 1	☐ Level 1	☐ Level 1
	☐ Level 2	☐ Level 2	☐ Level 2	☐ Level 2
	☐ Level 3	☐ Level 3	☐ Level 3	☐ Level 3

All exacerbations of COPD must be reported in the COPD Exacerbation section at the back of this module, using the corresponding onset date entered above. Corrective therapy for COPD exacerbations must be recorded in the COPD Medications or Procedures pages.



Protocol 207499/040		Patient Number 	Patient Initials 		Follow-Up Visit

RESOURCE UTILISATION FOR COPD EXACERBATIONS

If the patient has received any COPD exacerbation related medical care since the previous visit, please complete the COPD Resource Utilisation section at the back of this module.

DIARY CARD REVIEW

*Review the diary card for illegible/incomplete entries **in the presence of the patient.***

ADVERSE EXPERIENCES

If there have been any adverse experiences excluding COPD exacerbations (these are recorded in the COPD Exacerbation section) observed or elicited by the following direct question to the patient: "Have you felt different in any way since the last visit", please record details in the Adverse Experience section at the back of this module. The patient should refer to the notes in their diary when answering this question.

CONCOMITANT MEDICATION

If there has been any change in the patient's concomitant medication excluding treatment for COPD exacerbations (this is recorded in the COPD Exacerbations section) since the last visit, please record details in the Concomitant Medication section at the back of this module.

MEDICAL PROCEDURES

If there have been any non-medication, therapeutic, diagnostic or surgical procedures excluding those for COPD exacerbations (these are recorded in the COPD exacerbations section) performed since the last visit, please record details in the Medical Procedures section at the back of this module.

PHYSICAL EXAMINATION (INCLUDING RESPIRATORY EXAMINATION)

Only perform a Physical Examination if there were abnormalities at the previous visit.

Was this test performed ?

- ☐ No
☐ Yes

Has there been a clinically significant worsening in the patient's physical condition since the previous examination ?

- ☐ No
☐ Yes → *If 'Yes' record details in the Adverse Experience section at the back of this module.*



Page 661

Protocol 207499/040		Patient Number 	Patient Initials 		Follow-Up Visit

SMOKING STATUS

Does the patient currently smoke ?

☐ No☐ Yes → If 'Yes' please record the average number of cigarettes per day : **PULMONARY REHABILITATION PROGRAMME**

Has the patient entered a Pulmonary Rehabilitation Programme since the last visit ?

☐ No☐ Yes**LABORATORY TESTS***Only perform if there were abnormalities at the previous assessment.*

Was this test performed ?

☐ No☐ Yes*Please take blood samples for haematology and blood chemistry. Please refer to the instructions on the SBCL shipping form and manual.*Blood Sample Date
Day Mth Yr*Attach a label from the 'Routine/Unscheduled' laboratory requisition form used at this visit in the space below.*

Attach label here

Are there any **clinically significant worsenings** since the previous visit ?☐ No☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*Place the SBCL laboratory report in the plastic wallet at the back of this module.*



Protocol 207499/040		Patient Number 	Patient Initials 		Follow-Up Visit

URINALYSIS

Only required if abnormal at previous assessment.

Was this test performed ?

- ☐ No
☐ Yes

Please perform urinalysis using the dipstick provided by SBCL and record the results in the patient notes.

Urine Sample Date
 Day Mth Yr

Are the dipstick results negative?

- ☐ No ➔ *If 'No' please send the sample to SBCL for microscopy*
☐ Yes

Are there any **clinically significant worsenings** since the last visit on the SBCL report?

- ☐ No
☐ Yes ➔ *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

PREGNANCY TEST

Is the patient a female of child-bearing potential ?

- ☐ No
☐ Yes ➔ *If 'Yes' please perform a urine pregnancy test.*

Is the patient pregnant?

- ☐ No
☐ Yes ➔ *If 'Yes' please enter details in the Adverse Experience section.*



Protocol 207499/040		Patient Number 	Patient Initials 		Follow-Up Visit

FAECAL OCCULT BLOOD TEST

Record the results of the faecal occult blood tests.

Test	Date of Collection	Was the faecal occult blood test positive?
	Day Mth Yr	
1		☐ No ☐ Yes
2		☐ No ☐ Yes
3		☐ No ☐ Yes

Are these findings clinically significant ?

☐

No

☐

Yes



If 'Yes' record details in the Adverse Experience section at the back of this module.



Protocol 207499/040		Patient Number 	Patient Initials 		Follow-Up Visit

INVESTIGATOR INSTRUCTIONS

The following procedures must be performed more than 2 hours after the patient's last short-acting beta-2 agonist administration or more than 12 hours after the last long-acting beta-2 agonist.

VITAL SIGNS

After Sitting for 5 Minutes	
Blood Pressure (mmHg) systolic / diastolic	Heart Rate (beats/min)

Are there any **clinically significant worsenings** since the last visit ?

☐ No

☐ Yes → *If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section at the back of this module.*

12 LEAD ELECTROCARDIOGRAM

An ECG is only required if there were abnormalities at the previous assessment.

Was this test performed ?

☐ No

☐ Yes

The ECG should be performed after the patient has been semi-supine for 5 minutes

Date ECG performed:
Day Mth Yr

Were any clinically significant changes noted since the last visit ?

☐ No

☐ Yes → ☐ Improvement

☐ Worsening → *Enter details in the Adverse Experience section at the back of this module.*

Place the ECG trace in the plastic wallet at the back of this module.



Protocol 207499/040		Patient Number 	Patient Initials 		Follow-Up Visit

PULMONARY FUNCTION TESTS

Pulmonary function tests will be assessed more than 2 hours after the last dose of short-acting beta-2 agonists and / or anticholinergic medications and / or more than 12 hours after the last long-acting beta-2 agonists.

Measure the patient's pulmonary function three times using the spirometer provided by SB. (N.B. please follow instructions detailed in the Spirometry Manual). For each set of three FEV₁ measurements, one FEV₁ must be within 10% of the highest.

Please confirm that the pulmonary function tests were performed

☐

Performed

Place the spirometry report in the plastic wallet at the back of this module.

ADVERSE EXPERIENCES (Non-serious)**DEFINITIONS****INTENSITY (Maximum)**

MILD	<i>Adverse experience which is easily tolerated</i>
MODERATE	<i>Adverse experience sufficiently discomforting to interfere with daily activity</i>
SEVERE	<i>Adverse experience which prevents normal everyday activities</i>

RELATIONSHIP TO INVESTIGATIONAL DRUG

NOT RELATED	<i>The adverse experience is definitely not related to the test drug</i>
UNLIKELY	<i>There are other more likely causes and the drug is not suspected as a cause</i>
SUSPECTED (REASONABLE POSSIBILITY)	<i>A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug</i>
PROBABLE	<i>There probably is a direct cause and effect relationship between the adverse experience and the study drug</i>

SERIOUS ADVERSE EXPERIENCE (SAE)

A SAE is any experience which is :-

- 1 - fatal
- 2 - life threatening
- 3 - disabling/incapacitating
- 4 - results in hospitalisation (excluding elective surgery or routine clinical procedures)
- 5 - prolongs a hospital stay
- 6 - associated with congenital abnormality
- 7 - cancer
- 8 - associated with overdose
- 9 - In addition any event which the investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug should be reported as a serious event

IF A SAE OCCURS, PLEASE GO TO THE SAE SECTION IMMEDIATELY AND FOLLOW THE INSTRUCTIONS GIVEN THERE

Use each form for a maximum of two experiences

PLEASE REMEMBER ALL QUESTIONS ON ADVERSE EXPERIENCES FORM SHOULD BE COMPLETED



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Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Do you feel different in any way since starting the treatment or since the previous module?" Provide the diagnosis **not** symptoms where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbation section.

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the SAE section (See opposite for definitions of an SAE).

If no adverse experiences occurred since the previous module, please sign form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
End Date and Time (If ongoing please leave blank)	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy <i>If 'Yes', record details in the Concomitant Medication and / or Medical Procedures section</i> ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Mth Yr	



Page 667

Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Do you feel different in any way since starting the treatment or since the previous module?" Provide the diagnosis **not** symptoms where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbation section.

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the SAE section (See opposite for definitions of an SAE).

If no further adverse experiences or changes in adverse experiences occurred since the previous module, please sign form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	 Day Mth Yr 24hr:min	 Day Mth Yr 24hr:min
End Date and Time (If ongoing please leave blank)	 Day Mth Yr 24hr:min	 Day Mth Yr 24hr:min
Outcome <i>If patient died, STOP: go to SAE section and follow instructions given there</i> ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy <i>If 'Yes', record details in the Concomitant Medication and / or Medical Procedures section</i> ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE ?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Mth Yr	



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Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

ADVERSE EXPERIENCES (Non-serious)

Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Do you feel different in any way since starting the treatment or since the previous module?" Provide the diagnosis **not** symptoms where possible. One adverse experience per column.

Do not record COPD exacerbations here, record them in the COPD Exacerbation section.

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the SAE section (See opposite for definitions of an SAE).

If no further adverse experiences or changes in adverse experiences occurred since the previous module, please sign form below and mark this box. ☐

Adverse Experience (please print clearly)		
For SmithKline Beecham		
Onset Date and Time	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
End Date and Time (If ongoing please leave blank)	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
Outcome If patient died, STOP: go to SAE section and follow instructions given there ←	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication and / or Medical Procedures section ←	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE ?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Mth Yr	



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]		

CONCOMITANT MEDICATION

Record any changes in concomitant medication taken since the previous module.
(Please write using BLOCK CAPITALS)

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

☐ No concomitant medication changes since the previous module

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experience section using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the start and end date.

Drug Name (Trade name preferred)	Unit Dose (e.g. 500mg)	Frequency (e.g. bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of a diagnosis)	Start Date (be as precise as possible)			End Date (or if continuing mark box)			▼
					Day	Mth	Yr	Day	Mth	Yr	
					[][][]	[][][]	[][][]	[][][]	[][][]	[][][]	☐
For SB											
					[][][]	[][][]	[][][]	[][][]	[][][]	[][][]	☐
For SB											
					[][][]	[][][]	[][][]	[][][]	[][][]	[][][]	☐
For SB											
					[][][]	[][][]	[][][]	[][][]	[][][]	[][][]	☐
For SB											
					[][][]	[][][]	[][][]	[][][]	[][][]	[][][]	☐
For SB											
					[][][]	[][][]	[][][]	[][][]	[][][]	[][][]	☐
For SB											
					[][][]	[][][]	[][][]	[][][]	[][][]	[][][]	☐
For SB											
					[][][]	[][][]	[][][]	[][][]	[][][]	[][][]	☐
For SB											

* For Route, see tab for acceptable abbreviations.



Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

CONCOMITANT MEDICATION - Continued

Do not record any medication taken for COPD exacerbations in this section. Record all COPD exacerbation medication in the COPD Exacerbation section.

Any new medical illness/diagnosis (or symptoms in the absence of a diagnosis) should be recorded in the Adverse Experience section using the same terminology.

If a medication was marked 'Continuing' at a previous visit, but has since had a dosage change or has been stopped, it must be recorded as a change below with the start and end date.

Drug Name (Trade name preferred)	Unit Dose (e.g. 500mg)	Frequency (e.g. bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of a diagnosis)	Start Date (be as precise as possible)			End Date (or if continuing mark box)		
					Day	Mth	Yr	Day	Mth	Yr
For SB										
For SB										
For SB										
For SB										
For SB										
For SB										
For SB										
For SB										
For SB										

* For Route, see tab for acceptable abbreviations.



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][][]	Patient Initials [][][][]	Visit Date Day Mth Yr [][][][][]	

MEDICAL PROCEDURES (Excluding treatment for COPD exacerbations)

Do not record procedures used to treat COPD exacerbations here, record them in the COPD Exacerbations section.

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed since the previous module ?

☐ No

☐ Yes —▶ If 'Yes', please record details below using standard medical terminology

All indications for procedures should be recorded in the Adverse Experience section.

Procedure	Indication	Procedure Start Date			Procedure End Date		
		Day	Mth	Yr	Day	Mth	Yr
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							
		[][]	[][]	[][]	[][]	[][]	[][]
For SB							



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Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy. All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages.**

If no COPD Exacerbations since the previous module, please sign form below and mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
End Date and Time (If ongoing please leave blank)	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
Outcome If patient died, STOP: go to SAE COPD Exacerbation pages	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent No. of episodes ☐ Constant	☐ Intermittent No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures section	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE ?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____		Date : Day Mth Yr



Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy. All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages.**

If no further COPD Exacerbations or changes to COPD Exacerbations have occurred since the previous study, please sign form below and mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
End Date and Time (If ongoing please leave blank)	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
Outcome If patient died, STOP: go to SAE COPD Exacerbation pages	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent ☐ No. of episodes ☐ Constant	☐ Intermittent ☐ No. of episodes ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures section	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE ?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Mth Yr	



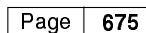
Protocol 207499/040	Centre Number 	Patient Number 	Patient Initials 		

DETAILS OF COPD EXACERBATIONS

An **exacerbation of COPD** is defined as a worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids and other bronchodilator therapy. All exacerbations of COPD since the previous module should be recorded below, except for those that fulfil the criteria for a Serious Adverse Experience (SAE). **COPD exacerbations that are SAEs must be recorded in the Serious Adverse Experience COPD Exacerbation pages.**

If no further COPD Exacerbations or changes to COPD Exacerbations have occurred since the previous study, please sign form below and mark this box. ☐

Adverse Experience	COPD EXACERBATION	COPD EXACERBATION
For SmithKline Beecham		
Onset Date and Time	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
End Date and Time (If ongoing please leave blank)	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
Outcome If patient died, STOP: go to SAE COPD Exacerbation pages	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course	☐ Intermittent ☐ Constant	☐ Intermittent ☐ Constant
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the COPD Medication and / or Medical Procedures section	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE ?	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Mth Yr	



Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date
207499/040				
				Day Mth Yr

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience	COPD Exacerbation	➤ Specify reason(s) for considering this a serious AE. Mark all that apply. 1 2 3 4 5 6 7 8 9 ☐ fatal ☐ life threatening ☐ disabling/incapacitating ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) ☐ hospitalisation prolonged ☐ congenital abnormality ☐ cancer ☐ overdose ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	Day Mth Yr 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	Day Mth Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent ➤ No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate ? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased) ☐ Yes ☐ No If yes, did SAE recur ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	➤ Assessment The SAE is probably associated with : ☐ Protocol design or procedures (but not to study drug) <i>Please specify</i> _____ ☐ Another condition (eg, condition under study, intercurrent illness) <i>Please specify</i> _____ ☐ Another drug <i>Please specify</i> _____
Corrective Therapy <i>If 'Yes', record details in the COPD Medication or Procedures pages</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)

Relevant Laboratory Data

Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

If applicable, was randomisation code broken at investigational site ? ☐ No ☐ Yes

Randomisation / Study Medication Number : [][][][][]

Investigator's Signature : _____
(confirming that the above data are accurate and complete)

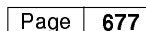
Date [][][][][]
Day Mth Yr

Please PRINT name _____

SB Medical Monitor's Signature : _____

Date [][][][][]
Day Mth Yr

Please PRINT name _____



Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date
207499/040				DayMthYr

Person Reporting SAE <i>(Please print clearly)</i>		AEGIS Number
Serious Adverse Experience	COPD Exacerbation	➤ Specify reason(s) for considering this a serious AE. Mark all that apply. 1 2 3 4 5 6 7 8 9 ☐ fatal ☐ life threatening ☐ disabling/incapacitating ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) ☐ hospitalisation prolonged ☐ congenital abnormality ☐ cancer ☐ overdose ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	Day Mth Yr 24hr:min	
End Date and Time <i>(If ongoing please leave blank)</i>	Day Mth Yr 24hr:min	
Outcome <i>If patient died, please complete Form D</i>	☐ Resolved ☐ Ongoing ☐ Died	
Experience Course	☐ Intermittent ➤ No. of episodes ☐ Constant	
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	Did the SAE abate ? ☐ Yes ☐ No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased) ☐ Yes ☐ No If yes, did SAE recur ☐ Yes ☐ No
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	➤ Assessment The SAE is probably associated with : ☐ Protocol design or procedures (but not to study drug) <i>Please specify</i> _____ ☐ Another condition (eg, condition under study, intercurrent illness) <i>Please specify</i> _____ ☐ Another drug <i>Please specify</i> _____
Corrective Therapy <i>If 'Yes', record details in the COPD Medication or Procedures pages</i>	☐ Yes ☐ No	
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No	



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) - COPD Exacerbation (cont)

Relevant Laboratory Data

Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

If applicable, was randomisation code broken at investigational site ? ☐ No ☐ Yes

Randomisation / Study Medication Number : [][][][][]

Investigator's Signature : _____ **Date**

Day Mth Yr

(confirming that the above data are accurate and complete)

Please PRINT name _____

SB Medical Monitor's Signature : _____ **Date**

Day Mth Yr

Please PRINT name _____

Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]		

MEDICATION FOR COPD EXACERBATIONS

Has the patient taken any medication for COPD exacerbations since the previous module ?

☐

No

☐

Yes → If 'Yes', please record details below

Drug Name (Trade name preferred)	Unit Dose (e.g. 500mg)	Frequency (e.g. bid, prn)	Route*	Medical Illness/ Diagnosis (or symptom in absence of a diagnosis)	Start Date (be as precise as possible) Day Mth Yr	End Date (or if continuing mark box) Day Mth Yr	
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							
				COPD EXACERBATION	[][][][][]	[][][][][]	☐
For SB							

* For Route, see General Instructions for acceptable abbreviations.



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]		

MEDICAL PROCEDURES FOR COPD EXACERBATIONS

Have any non-medication, therapeutic, diagnostic or surgical procedures been performed for COPD exacerbations since the previous module ?

☐ No

☐ Yes —▶ If 'Yes', please record details below using standard medical terminology

Procedure	Indication	Procedure Start Date			Procedure End Date		
		Day	Mth	Yr	Day	Mth	Yr
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							
	COPD EXACERBATION	[][]	[][]	[][]	[][]	[][]	[][]
For SB							



Protocol 207499/040	Centre Number [][][][]	Patient Number [][][][][][]	Patient Initials [][][][][]		

HEALTHCARE RESOURCE UTILISATION FOR COPD EXACERBATIONS

Complete this form for any **COPD exacerbation related medical care** the patient received since the previous module

Physician Visits (i.e., COPD care excluding scheduled protocol visits)

☐ There were no physician visits since the previous module

Date of Visit			Reason for Visit
Day	Mth	Yr	

Emergency Room (ER)/Urgent Care Visits/Casualty Department Procedures (i.e., lung surgery)

☐ There were no Emergency Room/Urgent Care Visits/Casualty Department Procedures since previous module

Date of Visit			Reason for Visit	Patient Admitted from ER ?	
				Yes	No
Day Mth Yr		☐		☐	
		☐		☐	
		☐		☐	
		☐		☐	
		☐		☐	
		☐		☐	
		☐		☐	



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]		

HEALTHCARE RESOURCE UTILISATION FOR COPD EXACERBATIONS - continued

Hospitalisations (also record details of any hospitalisations in the Serious Adverse Experience - COPD Exacerbation section)

☐ There were no hospitalisations since the previous module

Date of Admission			Date of Discharge			Reason for Admission
Day	Mth	Yr	Day	Mth	Yr	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	

Intensive Care Unit (ICU) stays (did the patient stay in the ICU during any of the above hospitalisations?)

☐ There were no ICU stays since the previous module

Date Admitted to ICU			Date Discharged from ICU			Reason for ICU Admission
Day	Mth	Yr	Day	Mth	Yr	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	

Lost Work Days (i.e., days patient missed work due to COPD excluding scheduled protocol visits)

☐ There were no lost work days since the previous module

Start Date			Stop Date			Reason for Absence
Day	Mth	Yr	Day	Mth	Yr	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	
[][]	[][]	[][]	[][]	[][]	[][]	



Protocol 207499/040	Centre Number <table border="1"><tr><td></td><td></td><td></td></tr></table>				Patient Number <table border="1"><tr><td></td><td></td><td></td><td></td><td></td></tr></table>								

MODULE 45

MODULE 45: Study Conclusion.

CRF Pages: 683

Unprocessed forms: Within this module the following occur which will generate attachments that need to be brought in-house.

None



Protocol	Centre Number	Patient Number	Patient Initials		
207499/040					

STUDY CONCLUSION

Did the patient complete the study as planned ? (i.e. has the patient stopped the study because the product has been registered or because the sponsor has terminated the study).

☐ Yes

☐ No → If 'No' please mark the **PRIMARY** cause of withdrawal.

1	☐ Adverse experience (complete AE form)
2	☐ Insufficient therapeutic effect
3	☐ Protocol deviation (including non-compliance)
4	☐ Lost to follow-up
5	☐ Other - specify: _____

Date of Final Visit

Day	Mth	Yr

Date of Final Dose

Day	Mth	Yr

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data on this case report form and that all information is complete and accurate.

Investigator's Signature _____

Date

Day	Mth	Yr

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EXPERIENCES (SAE)

SAEs MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS

COMPLETE THE SAE PAGES OPPOSITE

Please complete these pages as fully and accurately as possible in order to minimise the time you spend dealing with data queries

If the SAE is still ongoing at the time of reporting, please leave 'Experience Course' blank and update it later

SIGN AND DATE THE SAE PAGE**PLEASE ENSURE THAT ALL OF THE INFORMATION ON THE FOLLOWING CRF PAGES IS COMPLETE**

- Demography
- Significant Medical/Surgical History and Physical Examination
- Study Medication Record
- Concomitant Medication
- Form D (if applicable)

PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE

(Do not separate the NCR pages)

FAX A COPY OF THE SAE PAGES AND ALL OF THE CRF PAGES SPECIFIED ABOVE TO :

Your local SB CRA/Medical Monitor (see Investigator Site File for appropriate fax number)

If no photocopier OR fax is available please telephone your local SB CRA/Medical monitor within 24 hours



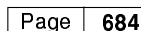
Protocol	Centre Number	Patient Number			
207499/040					

MOD46 & MOD47 - SERIOUS ADVERSE EXPERIENCES

MOD46 & 47: Serious Adverse Experiences

MOD46 : 684, 685

MOD47 : 686, 687



Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date
207499/040				Day Mth Yr

Person Reporting SAE _____ (Please print clearly)		AEGIS Number . 	
Serious Adverse Experience (Please print clearly)		➤ Specify reason(s) for considering this a serious AE. Mark all that apply.	
For SmithKline Beecham		1 ☐ fatal 2 ☐ life threatening 3 ☐ disabling/incapacitating 4 ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) 5 ☐ hospitalisation prolonged 6 ☐ congenital abnormality 7 ☐ cancer 8 ☐ overdose 9 ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution	
Onset Date and Time	Day Mth Yr 24hr:min		
End Date and Time (If ongoing please leave blank)	Day Mth Yr 24hr:min		
Outcome If patient died, please complete Form D	☐ Resolved ☐ Ongoing ☐ Died		
Experience Course	☐ Intermittent ➤ No. of episodes ☐ Constant		
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe		
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped		
Relationship to Investigational Drug	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable		
Corrective Therapy If 'Yes', record details in the Concomitant Medication section	☐ Yes ☐ No		
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No		



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data**

Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

If applicable, was randomisation code broken at investigational site ? ☐ No ☐ Yes

Randomisation / Study Medication Number : [][][][][]

Investigator's Signature : _____ **Date**

Day Mth Yr

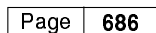
(confirming that the above data are accurate and complete)

Please PRINT name _____

SB Medical Monitor's Signature : _____ **Date**

Day Mth Yr

Please PRINT name _____



Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date
207499/040				
				Day Mth Yr

Person Reporting SAE						
(Please print clearly)						
Serious Adverse Experience	AEGIS Number					
(Please print clearly)						
For SmithKline Beecham						
Onset Date and Time						
	Day	Mth	Yr	24hr:min		
End Date and Time						
(If ongoing please leave blank)	Day	Mth	Yr	24hr:min		
Outcome	Specify reason(s) for considering this a serious AE. Mark all that apply.					
If patient died, please complete Form D ←	☐ fatal ☐ life threatening ☐ disabling/incapacitating ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures) ☐ hospitalisation prolonged ☐ congenital abnormality ☐ cancer ☐ overdose ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution					
Experience Course	Intermittent → No. of episodes Constant					
Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe					
Action Taken with Respect to Investigational Drug	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped					
Relationship to Investigational Drug	☐ Not related } ☐ Unlikely } ☐ Suspected (reasonable possibility) ☐ Probable } Assessment					
Corrective Therapy	The SAE is probably associated with :					
If 'Yes', record details in the Concomitant Medication section ←	☐ Protocol design or procedures (but not to study drug) Please specify _____ ☐ Another condition (eg, condition under study, intercurrent illness) Please specify _____ ☐ Another drug Please specify _____					
Was patient withdrawn due to this specific SAE ?	☐ Yes ☐ No					



Protocol 207499/040	Centre Number [][][]	Patient Number [][][][][]	Patient Initials [][][][]	

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)**Relevant Laboratory Data**

Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			
	Day Mth Yr			

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

If applicable, was randomisation code broken at investigational site ? ☐ No ☐ Yes

Randomisation / Study Medication Number : [][][][][]

Investigator's Signature : _____ **Date**

Day Mth Yr

(confirming that the above data are accurate and complete)

Please PRINT name _____

SB Medical Monitor's Signature : _____ **Date**

Day Mth Yr

Please PRINT name _____



Page

G1

Protocol 207499/040	Centre Number [][][]	Patient Number 0 0 0 0 0	Patient Initials [][][][]	Assessment Date Day Month Year [][][][][][]	Supplemental Report

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE

Please record below those gastrointestinal symptoms (i.e., bloody or black stools, abdominal discomfort such as pain or cramps, diarrhoea, vomiting) which cause concern or interfere with usual activity (including eating and sleeping) at any time during the study.

Report this gastrointestinal symptom(s) to the SB Medical Monitor by telephone within 24 hours of the first assessment and fax the completed Supplemental Gastrointestinal Adverse Experience Report within 24 hours of the first assessment. Also, fax Demography, Medical History, Prior and Concomitant Medication, Alcohol and Smoking History, Vital Signs, Adverse Experience or Serious Adverse Experience; and all study medication CRF pages.

Date of Assessment:

[][]	[][]	[][]
Day	Month	Yr

 Person performing assessment
 (Please print clearly)

Signature: _____

Please mark (✓) the gastrointestinal symptom(s) that prompted the report:

[1] ☐ Black or bloody stool	[4] ☐ Diarrhoea
[2] ☐ Abdominal discomfort	[5] ☐ Vomiting
[3] ☐ Other, specify: _____	

Record date and time of last dose of study medication prior to onset of GI symptom(s).

[][][][]	[][][][]
Day Month Yr	24hr:min

Was this dose taken with food?

- ☐ No
☐ Yes



Page	G2

Protocol 207499/040	Centre Number <table border="1"><tr><td></td><td></td><td></td></tr></table>				Patient Number <table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>					Assessment Date Day Month Year <table border="1"><tr><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>							Supplemental Report
0	0	0	0	0																			

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE

SYMPTOM ASSESSMENT (Please refer to the gastrointestinal symptom(s) marked on page 1).

At the time of this assessment how do the symptom(s) checked on page 1 compare with the time of onset?

[1] ☐ Resolved	[1] ☐ Resolved	[1] ☐ Resolved
[2] ☐ Better	[2] ☐ Better	[2] ☐ Better
[3] ☐ Same	[3] ☐ Same	[3] ☐ Same
[4] ☐ Worse	[4] ☐ Worse	[4] ☐ Worse

Symptoms made better by: (mark (✓) all that apply)

[1] ☐ Rest	[1] ☐ Rest	[1] ☐ Rest
[2] ☐ Meals	[2] ☐ Meals	[2] ☐ Meals
[3] ☐ Leaning forward with flexed trunk	[3] ☐ Leaning forward with flexed trunk	[3] ☐ Leaning forward with flexed trunk
[4] ☐ Medication (other than study medication), specify: _____	[4] ☐ Medication (other than study medication), specify: _____	[4] ☐ Medication (other than study medication), specify: _____
[5] ☐ Bowel Movement	[5] ☐ Bowel Movement	[5] ☐ Bowel Movement
[6] ☐ Physical Movement	[6] ☐ Physical Movement	[6] ☐ Physical Movement
[7] ☐ Other, specify: _____	[7] ☐ Other, specify: _____	[7] ☐ Other, specify: _____
[8] ☐ None of the above	[8] ☐ None of the above	[8] ☐ None of the above

Symptoms made worse by: (mark (✓) all that apply)

[1] ☐ Meals	[1] ☐ Meals	[1] ☐ Meals
[2] ☐ Lying supine	[2] ☐ Lying supine	[2] ☐ Lying supine
[3] ☐ Bowel Movement	[3] ☐ Bowel Movement	[3] ☐ Bowel Movement
[4] ☐ Cough	[4] ☐ Cough	[4] ☐ Cough
[5] ☐ Stress	[5] ☐ Stress	[5] ☐ Stress
[6] ☐ Alcohol	[6] ☐ Alcohol	[6] ☐ Alcohol

continued.....

continued.....

continued.....

Page **G3**

Protocol 207499/040	Centre Number [][][]	Patient Number 0 0 0 0 0	Patient Initials [][][][]	Assessment Date Day Month Year [][][][][][]	Supplemental Report

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE**SYMPTOM ASSESSMENT (continued)**

Continued from page 2:

Symptoms made worse by: (mark (✓) all that apply)

[7] ☐ Medication (other than study medication), specify: _____

[7] ☐ Medication (other than study medication), specify: _____

[7] ☐ Medication (other than study medication), specify: _____

[8] ☐ Physical Movement

[8] ☐ Physical Movement

[8] ☐ Physical Movement

[9] ☐ Other, specify: _____

[9] ☐ Other, specify: _____

[9] ☐ Other, specify: _____

[10] ☐ None of the above

[10] ☐ None of the above

[10] ☐ None of the above

Has the patient been drinking alcohol within the last 48 hours?

☐ No

☐ Yes → If 'Yes' record number of units (a unit of alcohol = 25cl (or half a pint) of beer, a medium-sized glass of wine (125ml) or a measure (24ml) of spirits) [][]

If the patient took a new concomitant medication or changed the dose of a continuing medication, please record this medication in the concomitant medication section of the CRF.

Abdominal pain or discomfort

If the patient has abdominal pain or discomfort, please complete the following pain assessment.

☐ Not Applicable; patient did not report abdominal pain or discomfort.

Location of pain or discomfort:

Schematic of Abdomen

RIGHT			LEFT		
1	2	3			
4	5	6			
7	8	9			

Check the box(es) below that corresponds to the location of abdominal pain or discomfort as shown on the schematic of the abdomen to the right.

[1] ☐ Right Hypochondriac [2] ☐ Epigastric [3] ☐ Left Hypochondriac

[4] ☐ Right Lateral [5] ☐ Umbilical [6] ☐ Left Lateral

[7] ☐ Right Inguinal [8] ☐ Suprapubic [9] ☐ Left Inguinal



Protocol	Centre Number			Patient Number					Patient Initials				Assessment Date			Supplemental Report
													Day	Month	Year	
207499/040				0	0	0	0	0								

SYMPTOM ASSESSMENT (continued)

Onset of pain or discomfort:

[1] ☐ Sudden

[2] ☐ Gradual

[3] ☐ Other, specify:

Quality of pain or discomfort (*mark (✓) all that apply*):

[1] Sharp

[2] ☐ Dull

[3] ☐ Achy

[4] ☐ Pulsatile

[5] Colicky

[6] ☐ Burning

[7] ☐ Gnawing

[8] ☐ Boring/drilling

[9] ☐ Cramping

[1 0] Other, specify:

Does pain or discomfort radiate?

☐ No

☐ Yes → *If 'Yes' please mark location(s) to which pain or discomfort radiates.*

[1] ☐ Abdominal Area (see schematic on page 3)
specify:

[4] ☐ Shoulder tip

[2] ☐ Back

[5] ☐ Other, specify:

[3] ☐ Groin

Temporal features of pain or discomfort:

[1] :Intermittent

[2] ☐ Continuous

[3] ☐ Other, specify:

Patient's subjective assessment of pain or discomfort intensity:

Grade pain or discomfort on a scale from 0 - 3 as follows:

Maximum since onset

At the time of this assessment

[1] ☐ Slight pain

[0] ☐ No pain

[2] ☐ Moderate Pain

[1] ☐ Slight pain

[3] ☐ Severe Pain

[2] ☐ Moderate Pain

[3] ☐ Severe Pain



Page G5

Protocol 207499/040	Centre Number [][][]	Patient Number 0 0 0 0 0	Patient Initials [][][][]	Assessment Date Day Month Year [][][][][][]	Supplemental Report

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE

SYMPTOM ASSESSMENT (Continued)

Stool Assessment

If the patient noticed black or bloody stool, please complete the following stool assessment. ☐ Not applicable

Is this the first time that the patient has noticed this? ☐ No ☐ Yes

How many bowel movements has the patient had in the last 24 hours? [][]

Has the patient had a nosebleed or bleeding gums in the last 48 hours? ☐ No ☐ Yes

If female, is bloody stool possibly menstrual or uterine in origin? ☐ No ☐ Yes ☐ Not applicable

Does the patient presently have haemorrhoids? ☐ No ☐ Yes

Is the patient taking NSAIDS/ASA? ☐ No ☐ Yes

Stool appearance (mark (✓) all that apply):

[1] ☐ Normal with red blood on outside	[5] ☐ No formed stool, only blood
[2] ☐ Normal with red blood mixed throughout	[6] ☐ Red toilet bowl water
[3] ☐ Black, tarry stool	[7] ☐ Other, specify: _____
[4] ☐ Normal stool with blood on toilet paper	

PHYSICAL EXAMINATION

General Appearance:

☐ Looks well

☐ Looks unwell → If unwell, specify: _____

Weight: [][][] . [] kg or: [][][] . [] lb

Present Absent

Abdominal tenderness ☐ ☐

Abdominal masses ☐ ☐

Peritoneal signs ☐ ☐

Other clinically significant physical examination findings, please specify: _____



Page G6

Protocol 207499/040	Centre Number [][][]	Patient Number 0 0 0 0 0	Patient Initials [][][]	Assessment Date Day Month Year [][][][][][]	Supplemental Report

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE

PHYSICAL EXAMINATION (<i>continued</i>)			
Orthostatic Vital Signs			
1st measurement		2nd measurement	
After 5 Minutes Supine		After sitting with Legs Dependent for 1 minute	
Blood Pressure mmHg systolic / diastolic	Heart Rate beats/min	Blood Pressure mmHg systolic / diastolic	Heart Rate beats/min
[][][] / [][][]	[][][]	[][][] / [][][]	[][][]
Are there any clinically significant worsenings since the previous assessment? ☐ No ☐ Yes → <i>If 'Yes' please record the findings and/or diagnosis in the Baseline Signs and Symptoms or the Adverse Experience page of the CRF.</i>			
Faecal Occult Blood			
[1] ☐ Positive	[1] ☐ Positive	[1] ☐ Positive	
[2] ☐ Negative	[2] ☐ Negative	[2] ☐ Negative	
Date of sample: [][][] Day Month Yr	Date of sample: [][][] Day Month Yr	Date of sample: [][][] Day Month Yr	



Page	G7

Protocol	Centre Number	Patient Number	Patient Initials	Assessment Date	Supplemental Report
207499/040		0 0 0 0 0		Day Month Year	

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE

Laboratory Sample	
Please take blood samples for haematology and blood chemistry (Section 8.1.2 of the protocol). Please refer to the instructions on the SBCL shipping form and manual.	
Blood Sample Date	Day Month Yr
Attach a label from the 'Unscheduled' laboratory requisition form used at this visit in the space to the right. Insert the SBCL laboratory report behind this page.	Attach label here
Are there any clinically significant worsenings since the previous assessment? ☐ No ☐ Yes → if 'Yes' please record the findings and/or diagnosis in the Adverse Experience section of the CRF.	



Page G8

Protocol 207499/040	Centre Number [][][]	Patient Number 0 0 0 0 0	Patient Initials [][][]	Assessment Date Day Month Year [][][][][][]	Supplemental Report

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE

Urinalysis

Please perform urinalysis using the dipstick provided by SBCL.

Urine Sample Date [][][][][][]
Day Month Yr

Was the sample sent to SBCL for microscopy due to a clinically significant abnormality with the dipstick test?

☐ No

☐ Yes → If 'Yes' are there any **clinically significant worsenings** since the previous assessment?

☐ No

☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience page of the CRF.

ADDITIONAL TESTS

Additional tests may be ordered at the discretion of the investigator. Please mark (✓) the additional tests that have been ordered.

[1] ☐ X-ray

[4] ☐ CT of abdomen

[2] ☐ Rectal/pelvic examination

[5] ☐ Stool for ova and parasites

[3] ☐ Ultrasound of the abdomen

[6] ☐ Other, specify: _____

Was the patient referred to a gastroenterologist or other specialist?

☐ No

☐ Yes

Please forward results when available and record tests in the Medical Procedures page of the CRF.

Investigator's Remarks: _____



Page G9

Protocol 207499/040	Centre Number [][][]	Patient Number 0 0 0 0 0	Patient Initials [][][][]	Assessment Date Day Month Year [][][][][][]	Supplemental Report

SUPPLEMENTAL REPORT FOR GASTROINTESTINAL ADVERSE EXPERIENCE

An adverse experience or serious adverse experience CRF form(s) must be completed.
Please check the appropriate box for the form(s) completed.

- ☐ Adverse experience(s) (see Protocol Section 8.1)
- ☐ Serious adverse experience(s) (see Protocol Section 8.5)

If adverse experience, please record in the Non-Serious Adverse Experience section of the CRF. If serious adverse experience, please record in the Serious Adverse Experience section of the CRF.

Adverse Experience(s) as recorded on Baseline Signs and Symptoms/
Adverse Experience or Serious Adverse Experience section.
(Please print clearly using same terminology and same onset date/time as in the CRF).

Onset Date and Time

-----	[][][][][][]	[][][]
	Day Month Yr	24hr:min
-----	[][][][][][]	[][][]
	Day Month Yr	24hr:min
-----	[][][][][][]	[][][]
	Day Month Yr	24hr:min

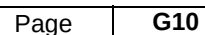
Investigator's Signature: -----

 Telephone
Number: () -- - -----

Please PRINT name: -----

SB Medical Monitor's Signature: -----

Please PRINT name: -----



Protocol	Centre Number			Patient Number					Patient Initials				Assessment Date			Supplemental Report
													Day	Month	Year	
207499/040				0	0	0	0	0								

Please submit COMPLETE Modules only. Do NOT submit whole blank modules.

Module	Module Description	Page Range	Modules		Missing Pages (if Applicable)
			Sent to DM	Unused	
MOD48	Supplemental Report for Gastrointestinal AE	G1 - G9	☐	☐	-----
MOD49	Supplemental Report for Gastrointestinal AE	G1 - G9	☐	☐	-----
MOD50	Supplemental Report for Gastrointestinal AE	G1 - G9	☐	☐	-----
MOD51	Supplemental Report for Gastrointestinal AE	G1 - G9	☐	☐	-----
MOD52	Supplemental Report for Gastrointestinal AE	G1 - G9	☐	☐	-----

If multiple modules are submitted together, please ensure they are sorted according to the order above

Site Monitor's Comments (e.g. protocol violations or deviations)

This image shows a full page of white paper with horizontal dashed lines, typical of primary school handwriting practice paper. The lines are evenly spaced and run across the entire width of the page. There are no margins, text, or other markings present.

Site Monitor's Signature _____ Date Submitted _____

Day Month Yr



Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 		Unscheduled Laboratory Tests

UNSCHEDULED LABORATORY TESTS

Visit number (or last **scheduled** visit number)

Please record here details of any **unscheduled** blood samples for haematology and blood chemistry (including serum beta-HCG for women of child-bearing potential) and/or urine sample for urinalysis (Section 5.4.8 of the protocol). Please refer to the instructions on the SBCL shipping form and manual.

Was a blood sample drawn ?

☐ No

☐ Yes → Blood Sample Date

Day	Month	Yr	

Was a urine sample obtained ?

☐ No

☐ Yes → If 'Yes' please perform urinalysis using the dipstick provided by SBCL.

Urine Sample Date

Day	Month	Yr	

Was the sample sent to SBCL for microscopy due to a clinically significant abnormality with the dipstick test ?

☐ No

☐ Yes

If a blood sample and / or urine sample are being sent to SBCL, attach a label from the 'Routine / Unscheduled' laboratory requisition form used at this visit in the space below.

Attach label here

Are there any **clinically significant worsenings** since the last visit ?

☐ No

☐ Yes → If 'Yes' please record the findings and/or diagnosis in the Adverse Experience section as appropriate, at the back of the module which contains the visit (or visit interval) at which these unscheduled tests were performed. Place the SBCL laboratory report in the plastic wallet at the back of the last scheduled visit.



Protocol 207499/040	Centre Number [][][]	Patient Number 0 0 0 0 0	Patient Initials [][][][]	Investigator _____

CRF TRACKING/REVIEW FORM

<i>Please submit COMPLETE Modules only. Do NOT submit whole blank modules.</i>					
Module	Module Description	Page Range	Modules		Missing Pages (if Applicable)
			Sent to DM	Unused	
MOD1	Visit 1, 2, 3, 4, AEs, Conmeds, Medical Procedures, COPD exacerbations, Resource Utilisation, Continuation / Withdrawal	1 - 54	☐	☐	_____
MOD2	SAE	55 - 56	☐	☐	_____
MOD3	SAE	57 - 58	☐	☐	_____
MOD4	Visit 5, 6, AEs, Conmeds, Medical Procedures, COPD exacerbations, Resource Utilisation, Continuation / Withdrawal	59 - 100	☐	☐	_____
QU1	Visit 6 SGRQ	688 - 692	☐	☐	_____
MOD5	SAE	101 - 102	☐	☐	_____
MOD6	SAE	103 - 104	☐	☐	_____
MOD7	Visit 7, 8, AEs, Conmeds, Medical Procedures, COPD exacerbations, Resource Utilisation, Continuation / Withdrawal	105 - 144	☐	☐	_____
MOD8	SAE	145 - 146	☐	☐	_____
MOD9	SAE	147 - 148	☐	☐	_____
<i>If multiple modules are submitted together, please ensure they are sorted according to the order above</i>					
Site Monitor's Comments (e.g. protocol violations or deviations) _____ _____ _____ _____ _____ _____					
Site Monitor's Signature _____			Date Submitted		[][][][][][] Day Month Yr



Protocol	Centre Number	Patient Number	Patient Initials	Investigator
207499/040		0 0 0 0		-----

CRF TRACKING/REVIEW FORM

Please submit COMPLETE Modules only. Do NOT submit whole blank modules.

Module	Module Description	Page Range	Modules		Missing Pages (if Applicable)
			Sent to DM	Unused	
MOD10	Visit 9, 10, AEs, Conmeds, Medical Procedures, COPD exacerbations, Resource Utilisation, Continuation / Withdrawal	149 - 190	☐	☐	-----
QU2	Visit 9 SGRQ	693 - 697	☐	☐	-----
QU3	Visit 9 SF36	698 - 702	☐	☐	-----
MOD11	SAE	191 - 192	☐	☐	-----
MOD12	SAE	193 - 194	☐	☐	-----
MOD13	Visit 11, 12, AEs, Conmeds, Medical Procedures, COPD exacerbations, Resource Utilisation, Continuation / Withdrawal	195 - 236	☐	☐	-----
MOD14	SAE	237 - 238	☐	☐	-----
MOD15	SAE	239 - 240	☐	☐	-----
MOD16	Visit 13, 14, AEs, Conmeds, Medical Procedures, COPD exacerbations, Resource Utilisation, Continuation / Withdrawal	241 - 280	☐	☐	-----
MOD17	SAE	281 - 282	☐	☐	-----
MOD18	SAE	283 - 284	☐	☐	-----

If multiple modules are submitted together, please ensure they are sorted according to the order above

Site Monitor's Comments (e.g. protocol violations or deviations)

Site Monitor's Signature _____ Date Submitted

Day	Month	Yr	



Protocol	Centre Number	Patient Number	Patient Initials	Investigator
207499/040		0 0 0 0 0		-----

CRF TRACKING/REVIEW FORM

Please submit COMPLETE Modules only. Do NOT submit whole blank modules.

Module	Module Description	Page Range	Modules		Missing Pages (if Applicable)
			Sent to DM	Unused	
MOD19	Visit 15, 16, AEs, Conmeds, Medical Procedures, COPD exacerbations, Resource Utilisation, Continuation / Withdrawal	285 - 326	☐	☐	-----
QU4	Visit 15 SGRQ	703 - 707	☐	☐	-----
QU5	Visit 15 SF36	708 - 712	☐	☐	-----
MOD20	SAE	327 - 328	☐	☐	-----
MOD21	SAE	329 - 330	☐	☐	-----
MOD22	Visit 17, 18, AEs, Conmeds, Medical Procedures, COPD exacerbations, Resource Utilisation, Continuation / Withdrawal	331 - 372	☐	☐	-----
MOD23	SAE	373 - 374	☐	☐	-----
MOD24	SAE	375 - 376	☐	☐	-----
MOD25	Visit 19, 20, AEs, Conmeds, Medical Procedures, COPD exacerbations, Resource Utilisation, Continuation / Withdrawal	377 - 416	☐	☐	-----
MOD26	SAE	417 - 418	☐	☐	-----
MOD27	SAE	419 - 420	☐	☐	-----

If multiple modules are submitted together, please ensure they are sorted according to the order above

Site Monitor's Comments (e.g. protocol violations or deviations)

Site Monitor's Signature _____ Date Submitted

Day	Month	Yr	



Protocol	Centre Number	Patient Number	Patient Initials	Investigator
207499/040		0 0 0 0 0		-----

CRF TRACKING/REVIEW FORM

Please submit COMPLETE Modules only. Do NOT submit whole blank modules.

Module	Module Description	Page Range	Modules		Missing Pages (if Applicable)
			Sent to DM	Unused	
MOD28	Visit 21, 22, AEs, Conmeds, Medical Procedures, COPD exacerbations, Resource Utilisation, Continuation / Withdrawal	421 - 462	☐	☐	-----
QU6	Visit 21 SGRQ	713 - 717	☐	☐	-----
QU7	Visit 21 SF36	718 - 722	☐	☐	-----
MOD29	SAE	463 - 464	☐	☐	-----
MOD30	SAE	465 - 466	☐	☐	-----
MOD31	Visit 23, 24, AEs, Conmeds, Medical Procedures, COPD exacerbations, Resource Utilisation, Continuation / Withdrawal	467 - 508	☐	☐	-----
MOD32	SAE	509 - 510	☐	☐	-----
MOD33	SAE	511 - 512	☐	☐	-----
MOD34	Visit 25, 26, AEs, Conmeds, Medical Procedures, COPD exacerbations, Resource Utilisation, Continuation / Withdrawal	513 - 552	☐	☐	-----
MOD35	SAE	553 - 554	☐	☐	-----
MOD36	SAE	555 - 556	☐	☐	-----

If multiple modules are submitted together, please ensure they are sorted according to the order above

Site Monitor's Comments (e.g. protocol violations or deviations)

Site Monitor's Signature ----- Date Submitted

Day	Month	Yr	



Protocol 207499/040	Centre Number 	Patient Number 0 0 0 0 0	Patient Initials 	Investigator _____

CRF TRACKING/REVIEW FORM

<i>Please submit COMPLETE Modules only. Do NOT submit whole blank modules.</i>					
Module	Module Description	Page Range	Modules		Missing Pages (if Applicable)
			Sent to DM	Unused	
MOD37	Visit 27, 28, AEs, Conmeds, Medical Procedures, COPD exacerbations, Resource Utilisation, Continuation / Withdrawal	557 - 598	☐	☐	_____
QU8	Visit 27 SGRQ	723 - 727	☐	☐	_____
QU9	Visit 27 SF36	728 - 732	☐	☐	_____
MOD38	SAE	599 - 600	☐	☐	_____
MOD39	SAE	601 - 602	☐	☐	_____
MOD40	Visit 29, 30, AEs, Conmeds, Medical Procedures, COPD exacerbations, Resource Utilisation, Continuation / Withdrawal	603 - 644	☐	☐	_____
MOD41	SAE	645 - 646	☐	☐	_____
MOD42	SAE	647 - 648	☐	☐	_____
MOD43	Early Withdrawal (EW) Visit	649 - 658	☐	☐	_____
QU10	SGRQ (EW Visit)	733 - 737	☐	☐	_____
QU11	SF36 (EW Visit)	738 - 742	☐	☐	_____
<i>If multiple modules are submitted together, please ensure they are sorted according to the order above</i>					
Site Monitor's Comments (e.g. protocol violations or deviations) _____ _____ _____ _____ _____ _____					
Site Monitor's Signature _____			Date Submitted		 Day Month Yr

Protocol	Centre Number	Patient Number	Patient Initials	Investigator
207499/040		0 0 0 0 0		-----

Please submit COMPLETE Modules only. Do NOT submit whole blank modules.

Module	Module Description	Page Range	Modules		Missing Pages (if Applicable)
			Sent to DM	Unused	
MOD44	Follow-Up Visit, AEs, Conmeds, Medical Procedures, COPD exacerbations, Resource Utilisation, Continuation / Withdrawal	659 - 682	☐	☐	-----
MOD45	Study Conclusion	683	☐	☐	-----
MOD46	SAE	684 - 685	☐	☐	-----
MOD47	SAE	686 - 687	☐	☐	-----
FORMD	Form D	n/a	☐	☐	-----
LABRET	Lab Retest	n/a	☐	☐	-----

If multiple modules are submitted together, please ensure they are sorted according to the order above

Site Monitor's Comments (e.g. protocol violations or deviations)

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Site Monitor's Signature _____ Date Submitted _____

Day Month Yr



Protocol	Centre Number	Patient Number	Patient Initials	Investigator
207499/040		0 0 0 0 0		-----

Please submit COMPLETE Modules only. Do NOT submit whole blank modules.

Module	Module Description	Page Range	Modules		Missing Pages (if Applicable)
			Sent to DM	Unused	
MOD48	Supplemental Report for Gastrointestinal AE	G1 - G9	☐	☐	-----
MOD49	Supplemental Report for Gastrointestinal AE	G1 - G9	☐	☐	-----
MOD50	Supplemental Report for Gastrointestinal AE	G1 - G9	☐	☐	-----
MOD51	Supplemental Report for Gastrointestinal AE	G1 - G9	☐	☐	-----
MOD52	Supplemental Report for Gastrointestinal AE	G1 - G9	☐	☐	-----

If multiple modules are submitted together, please ensure they are sorted according to the order above

Site Monitor's Comments (e.g. protocol violations or deviations)

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Site Monitor's Signature _____ Date Submitted _____

Day Month Yr



Protocol	Centre Number	Patient Number	Patient Initials	Investigator
207499/040		0 0 0 0 0		_____

CRF TRACKING/REVIEW FORM

Please submit COMPLETE Modules only. Do NOT submit whole blank modules.

Module	Module Description	Page Range	Modules		Missing Pages (if Applicable)
			Sent to DM	Unused	
MOD53	Visit 31, 32, AEs, Conmeds, Medical Procedures, COPD exacerbations, Resource Utilisation, Continuation / Withdrawal	743 - 782	☐	☐	_____
MOD54	SAE	783 - 784	☐	☐	_____
MOD55	SAE	785 - 786	☐	☐	_____
MOD56	Visit 33, 34, AEs, Conmeds, Medical Procedures, COPD exacerbations, Resource Utilisation, Continuation / Withdrawal	787 - 828	☐	☐	_____
QU12	Visit 33 SGRQ	743 - 747	☐	☐	_____
QU13	Visit 33 SF36	748 - 752	☐	☐	_____
MOD57	SAE	829 - 830	☐	☐	_____
MOD58	SAE	831 - 832	☐	☐	_____

If multiple modules are submitted together, please ensure they are sorted according to the order above

Site Monitor's Comments (e.g. protocol violations or deviations)

Site Monitor's Signature _____ Date Submitted

Day	Month	Yr	

SmithKline Beecham
Pharmaceuticals

PATIENT DIARY

This diary is a very important part of the study.

Remember:

- Complete the diary card if you feel different since starting the study medication.
- All visits should be in the morning between 10am and 12 noon, therefore on the day of your next visit do NOT take your morning dose of study medication before attending the clinic. In the exceptional case that your appointment has to be in the afternoon, please contact your doctor for instructions regarding your morning dose of study medication.
- Do NOT use your inhalers during the 2 hours before your next appointment unless you really have to.
- Do NOT smoke 2 hours before your next appointment.
- Bring all empty study medication bottles and any unused study medication to your next appointment.
- Bring this diary with you to your next appointment.
- If you experience gastrointestinal symptoms that interfere with your usual activities or cause concern please telephone the number below as soon as possible.

In an emergency, telephone :

name

at : -----
phone number

Date and time of next appointment

Day	Mth	Yr	24hr:min

CONFIDENTIAL

GM2003/00558/00
SB-207499/040

Date

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Protocol	Centre Number	Patient Number	Patient Initials												
207499/040	<table><tr><td></td><td></td><td></td></tr></table>				<table><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	<table><tr><td></td><td></td><td></td><td></td></tr></table>				
0	0	0	0	0											

CONFIDENTIAL





Page	688

Protocol	Centre Number	Patient Number	Patient Initials	Visit Date	Visit 6 Week 12
207499/040				Day Month Year	

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE (PAGE 1 OF 5)

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.



Protocol	Centre Number	Patient Number	Patient Initials	Visit Date	Visit 9 Week 24
207499/040				Day Month Year	

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE (PAGE 1 OF 5)

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials [][][][]		Visit 9 Week 24

SF - 36 (HEALTH STATUS QUESTIONNAIRE)

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Protocol	Centre Number	Patient Number	Patient Initials	Visit Date	Visit 15 Week 48
207499/040				Day Month Year	

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE (PAGE 1 OF 5)

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials 		Visit 15 Week 48

SF - 36 (HEALTH STATUS QUESTIONNAIRE)

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Protocol	Centre Number	Patient Number	Patient Initials	Visit Date	Visit 21 Week 72
207499/040				Day Month Year	

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE (PAGE 1 OF 5)

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Protocol 207499/040		Patient Number 0 0 0 0 0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						Visit 21 Week 72

SF - 36 (HEALTH STATUS QUESTIONNAIRE)

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Page	723

Protocol	Centre Number	Patient Number	Patient Initials	Visit Date	Visit 27 Week 96
207499/040				Day Month Year	

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE (PAGE 1 OF 5)

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Protocol 207499/040		Patient Number <table border="1"><tr><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr></table>	0	0	0	0	0	Patient Initials <table border="1"><tr><td></td><td></td><td></td><td></td></tr></table>						Visit 27 Week 96
0	0	0	0	0										

SF - 36 (HEALTH STATUS QUESTIONNAIRE)

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Protocol	Centre Number	Patient Number	Patient Initials	Visit Date	Early Withdrawal
207499/040				Day Month Year	

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE (PAGE 1 OF 5)

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Protocol		Patient Number	Patient Initials		Early Withdrawal
207499/040		0 0 0 0 0			

SF - 36 (HEALTH STATUS QUESTIONNAIRE)

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Protocol	Centre Number	Patient Number	Patient Initials	Visit Date	Enter Visit Number :
207499/040		0 0 0 0 0		Day Month Year	

ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE (PAGE 1 OF 5)

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Page	

Protocol		Patient Number	Patient Initials		Enter Visit Number :
207499/040		0 0 0 0 0			

SF - 36 (HEALTH STATUS QUESTIONNAIRE)

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LIST OF INVESTIGATORS FOR SB-207499/040 GM2003/00558/00

Investigators	Ctr	Investigational Site	City/State
Australia			
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Professor [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED] Australia [REDACTED]
Professor [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Professor [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED] Australia
Professor [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Professor [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Belgium			
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Prof [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

¹ Centre [REDACTED] Before study start Principal Investigator (PI) was Prof [REDACTED] At study start PI was Prof [REDACTED] and then back to Prof [REDACTED] 2 months into the study.

Investigators	Ctr	Investigational Site	City/State
Finland			
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
		Site moved in the beginning of this year to :	
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
France			
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Professor [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Investigators		Ctr	Investigational Site	City/State
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Professor	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Germany				
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

	Investigators	Ctr	Investigational Site	City/State
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Netherlands				
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Norway				
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
South Africa				
Professor	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Investigators		Ctr	Investigational Site	City/State
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Professor [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Spain				
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dra [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Investigators	Ctr	Investigational Site	City/State
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dra [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dra [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dr [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Investigators		Ctr	Investigational Site	City/State
Dra				
Dr				
Dr				
Dra.				
Dr				
Dr				
Dr				
Dr				
Dr				
Dr				
Dr				
Dr				
UK				
Dr				
Dr				

Investigators		Ctr	Investigational Site	City/State
Dr				
Dr				
Dr				
Dr				
Dr				
Dr				
Dr				
Dr				
Dr				

² Centre █████ Principal Investigator (PI) at study start was Dr █████ during the study this changed to Dr █████ She has now left and there is no nominated PI for the site than the individual GPs involved.

This section contained Principal Investigator's Curriculum Vitae and has been excluded to protect Principal Investigator privacy.

Sponsor Signatory Signature Page

STUDY TITLE: A Multicentre, Open-label Extension Study to Evaluate the Safety, Tolerability and Efficacy of Oral SB-207499 (15 mg twice daily) in Patients with Chronic Obstructive Pulmonary Disease (COPD). Final Report.

Study: SB-207499/040

Development Phase: III

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory:

[REDACTED]

Title of Sponsor Signatory:

Vice President, Respiratory Clinical
Development and Medical Affairs,
GlaxoSmithKline

Signed On behalf of

[REDACTED]

Dr [REDACTED]

Senior Director, Respiratory Clinical
Development and Medical Affairs,

GlaxoSmithKline

Signature:

[REDACTED]

Date:

28-4-04